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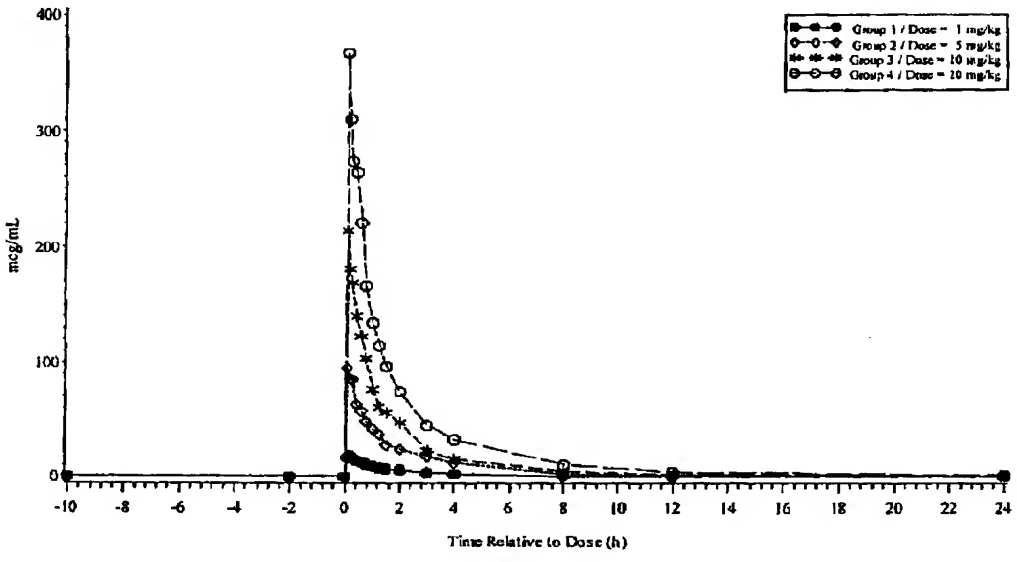
(54) Title: INTRAVENOUS FORMULATIONS OF PYRIDOXAL 5'-PHOSPHATE AND METHOD OF PREPARATION



(57) Abstract: The present invention provides a lyophilized formulation of pyridoxal 5'-phosphate and a method of making the same. The present invention also provides an injectable formulation of pyridoxal 5'-phosphate reconstituted from the lyophilized formulation. The present invention further provides uses of the lyophylized and injectable formulations.

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Title: Intravenous Formulations of Pyridoxal 5'-phosphate and Method of Preparation

Field of Invention

[0001] The present invention relates to pharmaceutical formulations of pyridoxal 5'-phosphate, and in particular formulations suitable for intravenous administration.

Background

[0002] Pyridoxal 5'-phosphate (P5P) is useful for the treatment and prevention of a variety of diseases such as hypertension, cerebrovascular disorders, cardiovascular disorders and diabetes. See for example US patent numbers 6,051,587; 6,417,204; 6,548,519; 6,586,414; 6,605,612; 6,667,315; 6,780,997; 6,677,356; 6,489,348; and 6,043,259.

[0003] Intravenous formulations of pyridoxal 5'-phosphate are known in the prior art. However, the stability of aqueous solutions of pyridoxal 5'-phosphate is poor. As well, it is highly light sensitive in solution, and to a lesser degree also in powder form. As such, prior art intravenous formulations of pyridoxal 5'-phosphate required the inclusion of preservatives for improving stability and for increasing shelf life. However, such preservatives often give rise to undesirable side effects and have not addressed the light sensitivity of pyridoxal 5'-phosphate. As well, such preservatives are often unsuitable for use in regulatory approval.

[0004] The present invention provides novel intravenous formulations of pyridoxal 5'-phosphate which are less susceptible to degradation and which do not require the inclusion of preservatives. The intravenous formulations exhibit improved pharmacokinetic profiles.

Summary of Invention

[0005] In one aspect, the present invention provides a lyophilized formulation of pyridoxal 5'-phosphate having been prepared by lyophilizing a frozen sterile aqueous solution of pyridoxal 5'-phosphate in a concentration higher than a supplement concentration and sodium hydroxide.

[0006] In an embodiment of the invention, the pH of the solution is between 7.0 and 7.3.

[0007] In another embodiment of the invention, the lyophilized formulation further comprises mannitol.

[0008] In a further aspect, the present invention provides an injectable formulation containing pyridoxal 5'-phosphate, reconstituted from a lyophilized formulation according to the invention, using a sterile carrier suitable for intravenous administration.

[0009] In an embodiment of the invention, the sterile carrier is water for injection.

[00010] In a further aspect, the present invention provides a process for preparing a lyophilized formulation of pyridoxal 5'-phosphate comprising the steps: (a) preparing a sterile solution comprising pyridoxal 5'-phosphate, sodium hydroxide, said solution having a pH between 7.0 and 7.3; (b) freezing the solution; and (c) lyophilizing the frozen solution.

[00011] In another embodiment of the invention, the sterile solution further comprises mannitol.

[00012] In another embodiment of the invention, the sterile solution contains pyridoxal 5'-phosphate in a concentration higher than a supplement concentration.

[00013] In a further aspect, the present invention provides a kit useful for preparing the injectable formulation according to the invention comprising instructions and in separate containers: (a) the lyophilized formulation of pyridoxal 5'-phosphate of according to the invention; and (b) a sterile carrier suitable for intravenous administration.

[00014] In an embodiment of the invention, the kit comprises water for injection as the sterile carrier.

[00015] In a further embodiment of the invention, the kit further comprises a container for said injectable formulation, said container sized to faciliate preparation of a selected volume and concentration of said formulation.

[00016] In a further aspect, the present invention provides use of a lyophilized formulation according to the invention for the preparation of an injectable formulation suitable for administration to patient in need of treatment with pyridoxal-5-phosphate.

[00017] In a further aspect, the present invention provides a method of treating a patient in need of treatment with pyridoxal-5-phosphate comprising intravenously administering the injectable formulation according to the invention

[00018] In a further aspect, the present invention provides a method of reducing the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of the injectable formulation according to the invention.

[00019] In a further aspect, the present invention provides use of an injectable formulation according to the invention for reduction of the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof.

[00020] In a further aspect, the present invention provides a method of treating a patient undergoing a surgical procedure in need of treatment with

pyridoxal-5-phosphate comprising intravenously administering the injectable formulation according to the invention.

[00021] In a further aspect, the present invention provides use of a lyophilized formulation according to the invention for the preparation of an injectable formulation suitable for administration to patient undergoing a surgical procedure in need of treatment with pyridoxal-5-phosphate.

[00022] In an embodiment of the invention, the surgical procedure is coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Brief Description of the Figures

[00023] Figure 1 is a line graph comparing the mean measured plasma pyridoxal 5'-phosphate concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00024] Figure 2 is a line graph comparing the mean baseline adjusted plasma pyridoxal 5'-phosphate concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00025] Figure 3 is a line graph comparing the mean baseline adjusted plasma pyridoxal 5'-phosphate log concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00026] Figure 4 is a line graph comparing the mean measured plasma pyridoxal concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00027] Figure 5 is a line graph comparing the mean baseline adjusted plasma pyridoxal concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00028] Figure 6 is a line graph comparing the mean baseline adjusted plasma pyridoxal log concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00029] Figure 7 is a line graph comparing the mean measured plasma 4-pyridoxic acid concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00030] Figure 8 is a line graph comparing the mean baseline adjusted plasma 4-pyridoxic acid concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00031] Figure 9 is a line graph comparing the mean baseline adjusted plasma 4-pyridoxic acid log concentration versus time for single intravenous dose of 1, 5, 10, and 20 mg/kg of plasma pyridoxal 5'-phosphate.

[00032] Figure 10 is a line graph comparing the baseline corrected plasma pyridoxal 5'-phosphate mean concentration versus time as measured on Day 1 and on Day 4.

[00033] Figure 11 is a line graph comparing the baseline corrected plasma pyridoxal 5'-phosphate ln transformed mean concentration versus time as measured on Day 1 and on Day 4.

[00034] Figure 12 is a line graph comparing the uncorrected plasma pyridoxal 5'-phosphate mean concentration versus time as measured on Day 1 and on Day 4.

[00035] Figure 13 is a line graph comparing the uncorrected plasma pyridoxal 5'-phosphate ln transformed mean concentration versus time as measured on Day 1 and on Day 4.

[00036] Figure 14 is a line graph comparing the plasma pyridoxal mean concentration versus time as measured on Day 1 and on Day 4.

[00037] Figure 15 is a line graph comparing the plasma 4-pyridoxic acid ln transformed mean concentration versus time as measured on Day 1 and on Day 4.

[00038] Figure 16 is a line graph comparing the plasma 4-pyridoxic acid mean concentration versus time as measured on Day 1 and on Day 4.

[00039] Figure 17 is a line graph comparing the plasma pyridoxal ln transformed mean concentration versus time as measured on Day 1 and on Day 4.

Detailed Description

[00040] The present invention provides novel lyophilized and injectable formulations of pyridoxal 5'-phosphate and uses thereof. The injectable formulations of pyridoxal 5'-phosphate are suitable for intravenous administration to patients in need of treatment with pyridoxal 5'-phosphate. The injectable formulations of the present invention have improved pharmacokinetics without any significant side effects. Intravenous administation of the injectable formulations of the present invention provides increased sustained plasma levels of pyridoxal 5'-phosphate as compared to prior art formulations.

[00041] Previous attempts to prepare a stable intravenous formulation of pyridoxal 5'-phosphate have required the addition of preservatives which were either potentially toxic or potentially carcinogenic. In the absence of preservatives, aqueous solutions of pyridoxal 5'-phosphate degrade rapidly and thus are unsuitable for intravenous administration. The present inventor has found novel lyophilized formulations of pyridoxal 5'-phosphate which can be reconstituted to prepare a stable injectable formulation which does not require the addition of any conventional preservative. Surprisingly, the stability of an intravenous formulation of pyridoxal 5'-phosphate is significantly increased, by lyophilizing the pyridoxal 5'-phosphate with mannitol prior to reconstitution in a suitable carrier. Furthermore, the intravenous formulations so prepared exhibit

improved stability without compromising the phermacokinetic properties of its active ingredient, and without any significant side effects.

[00042] The formulations of the present invention are particularly useful for the treatment of cardiovascular and cerebrovascular complications. Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are two of the most frequently performed procedures in North America. During the surgeries patients are infused with antiplatelet and antithrombotic therapies to reduce the frequency of ischemic complications. Specifically, the therapies used are heparin, abciximab and eptifibatide. They can be used alone or in combination with each other. The present invention provides formulations of pyridoxal 5'-phosphate which can be administered intravenously during CABG or PCI to further reduce ischemic complications.

[00043] The formulations according to the invention are also suitable for administration to stroke patients unable to swallow an oral form of pyridoxal 5'-phosphate such as a tablet. As well, in a hospital setting, an intravenous formulation of pyridoxal 5'-phosphate, as opposed to an oral formulation, provides the advantages of providing higher plasma levels of pyridoxal 5'-phosphate without inducing the gastric irritation, nausea, vomiting and diarrhea which can be associated with oral administration of pyridoxal 5'-phosphate. In addition, intravenous formulations achieve high plasma levels within minutes whereas an oral formulation may require hours to reach similar levels. This makes the intravenous formulation ideal for emergency situations (for example, treatment of MI or stroke, emergency PCI or bypass) in which oral administration is not possible or ideal.

Lyophilized Formulation of Pyridoxal 5'-phosphate and Method of Preparation

[00044] In one aspect, the present invention provides a lyophilized formulation of pyridoxal 5'-phosphate having been prepared by lyophilizing a frozen sterile aqueous solution of pyridoxal 5'-phosphate, sodium hydroxide and optionally, mannitol.

[00045] The lyophilized formulation of pyridoxal 5'-phosphate comprises a lyophilized sterile aqueous solution of pyridoxal 5'-phosphate in a concentration higher than a supplement concentration.

[00046] "Supplement concentration" as used herein is defined to mean a concentration which is intended for restoring a vitamin or metabolite level to a normal level in a person suffering from a vitamin or metabolite deficiency, and excludes a concentration which is suitable for increasing a vitamin or metabolite level to an above normal metabolic level.

[00047] The lyophilized formulation can be prepared using pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof. Both the monohydrate and the anhydrous forms of pyridoxal 5'-phosphate are suitable for preparation of the pharmaceutical compositions of the invention. The pyridoxal 5'-phosphate may be provided as salt forms with pharmaceutically compatible counterions such as but not limited, to citrate, tartate, bisulfate, etc. The pharmaceutically compatible salts may be formed with many acids, including but, not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. The salt forms tend to be more soluble in aqueous or other protonic solvents than the corresponding free base forms.

[00048] A first step in preparing the lyophilized formulation of pyridoxal 5'-phosphate is to prepare a sterile solution comprising pyridoxal 5'-phosphate and sodium hydroxide.

[00049] In preferred embodiment, the sterile solution has a pH of about between 7.0 and 7.3. The solution is prepared by first dissolving the pyridoxal 5'-phosphate and sodium hydroxide in a suitable amount of water and adjusting the pH.

[00050] The term "percentage weight per weight (% w/w)" as used herein refers to the weight percentage of the particular compound or carrier relative to the total weight of the composition of which the compound or carrier is a constituent of.

[00051] In an embodiment, the sterile solution will contain about 1 to 25 % w/w pyridoxal 5'-phosphate.

[00052] In a preferred embodiment, the sterile solution will contain about 1 to 15 % w/w pyridoxal 5'-phosphate.

[00053] In a further preferred embodiment, the sterile solution will contain about 1 to 10 % w/w pyridoxal 5'-phosphate.

[00054] In a still further preferred embodiment, the sterile solution will contain about 5 % w/w pyridoxal 5'-phosphate.

[00055] In another embodiment, the sterile solution will contain about 0.1 to 10 % w/w sodium hydroxide.

[00056] In a preferred embodiment, the sterile solution will contain about 0.5 to 5 % w/w sodium hydroxide.

[00057] In a further preferred embodiment, the sterile solution will contain about 0.5 to 3 % w/w sodium hydroxide.

[00058] In a still further preferred embodiment, the sterile solution will contain about 1.5 % w/w sodium hydroxide.

[00059] In another embodiment, the sterile solution may further comprise mannitol. In embodiments where the sterile solution includes mannitol, the sterile solution is prepared by first dissolving the pyridoxal 5'-phosphate and sodium hydroxide in a suitable amount of water and adjusting the pH, followed by dissolving the mannitol in the pyridoxal 5'-phosphate/sodium hydroxide solution. The resulting solution is then sterilized, for example, by filter sterilization.

[00060] In one embodiment, the sterile solution will contain about 0.2 to 10 % w/w mannitol.

[00061] In one embodiment, the sterile solution will contain about 0.5 to 5 % w/w mannitol.

[00062] In a preferred embodiment, the sterile solution will contain about 3 % w/w mannitol.

[00063] In a more preferred embodiment, the sterile solution will contain about 5 % w/w of pyridoxal 5'-phosphate, about 1.5 % w/w of sodium hydroxide and about 2.8% w/w of mannitol.

[00064] The sterilize solution may then be dispensed into sterile plastic or glass containers such as ampoules or vials in suitable volumes.

[00065] The amount of pyridoxal 5'-phosphate packaged into a single vial may vary between 25mg and 1000mg, between 50 and 1000 mg and more preferably between 100 and 750 mg. The amount of the sodium hydroxide and mannitol will depend on the amount of pyridoxal 5'-phosphate. In one embodiment of the invention, a single unit dosage form of the lyophilized formulation comprises about 250 mg of pyridoxal 5'-phosphate, 80.5 mg of sodium hydroxide, 150 mg of mannitol and 5.0 ml WFI (water for injection).

[00066] Once the sterile solution has been aliquoted into containers, the solution is frozen at temperature of between -20 and – 45 °C. The substantially frozen aqueous solution may be maintained at this temperature until lyophilization is commenced.

[00067] Lyophilization of the substantially frozen aqueous solution may be carried out involving, for example, both primary drying and secondary drying. Primary drying may be carried out via sublimation by using controlled application of vacuum and heat, for example under a substantial vacuum of about 0.1 to 0.5 Torr for sufficient time to effect removal of substantially all the frozen water and/or other solvent. Secondary drying is preferably carried out subsequently under a substantially similar vacuum to remove as much as possible of the last traces of adsorbed water or other solvent, thus providing a dry cake or powder.

[00068] The temperature at which primary drying is carried out ranges from -10 to 0 °C at the beginning of the process so as to maintain the solution in a substantially or completely frozen form. As the process proceeds and the product temperature reaches the desired shelf temperature, the primary drying phase is completed. The temperature at which secondary drying is carried out ranges from 25 to 35 °C in order to remove any adsorbed water and/or other solvent. The moisture content of the resulting cake or powder is preferably less than 2.5% by weight. Once the lyophilization has been completed, the sterile, plastic or glass container containing the lyophilized formulation may then be stoppered or sealed.

[00069] The resulting lyophilized formulation is physically and chemically stable when stored in low light conditions and at temperatures between 2 to 8 °C.

Injectable Formulation of Pyridoxal 5'-phosphate and Method of Preparation

[00070] In another aspect, the present invention provides an injectable formulation containing pyridoxal 5'-phosphate in a concentration higher than a supplement concentration, reconstituted from a lyophilized formulation according to the invention, using a sterile carrier suitable for intravenous administration. Preferably, the lyophilized formulation according to the invention is reconstituted in an appropriate volume of WFI (water for injection) to provide the injectable formulation. The resulting injectable formulation is particularly suitable for bolus administration. Preferably, the concentration of pyridoxal 5'-phosphate in the injectable formulation will be in the range of 1 to 100 mg/ml, 5 to 75 mg/ml, and more preferably between 10 and 50 mg/ml.

Kits for the Preparation of an Injectable Formulation of Pyridoxal 5'-phosphate

[00071] In a further aspect, the present invention provides a kit useful for preparing the injectable formulation according to the invention comprising

instructions for preparing the injectable formulation and in separate containers: (a) the lyophilized formulation of pyridoxal 5'-phosphate of according to the invention; and (b) a sterile carrier suitable for intravenous administration. In a preferred embodiment, the sterile carrier is WFI. In another preferred embodiment, the kit further comprises a container for the injectable formulation, said container sized to faciliate preparation of a selected volume and concentration of the injectable formulation.

[00072] The lyophilized formulation and the sterilized carrier can be aliquoted into volumes suitable for a single bolus injection. The lyophilized formulation and the sterilized carrier can be aliquoted into volumes suitable for extended administration. The kit can comprise a container, the container being sized to facilitate preparation of the formulation for injection to specified concentrations and volumes, without further measuring. The container can be a syringe body or suitable for use with a syringe.

Uses of Injectable Formulation of Pyridoxal 5'-phosphate

[00073] A limiting factor in the tolerance to high doses of pyridoxal 5'-phosphate is gastrointestinal discomfort characterized mainly by nausea and vomiting. The present invention provides novel injectable formulations suitable for the intravenous administration of high doses of pyridoxal 5'-phosphate with minimal gastrointestinal side effects associated with oral administration. The injectable formulations according to the invention overcome the stability issues of prior art intravenous formulations of pyridoxal 5'-phosphate. The stability of aqueous solutions of pyridoxal 5'-phosphate contained in the injectable formulations of the present invention are improved over the prior art pyridoxal 5'-phosphate formulations which are highly light sensitive in solution, and to a lesser degree in powder form. The intravenous formulations of according to the invention do not require or require to a lesser degree, the inclusion of preservatives for improving stability and for increasing shelf life, as compared to the prior art formulations.

[00074] Thus a method of treating a patient in need of treatment with pyridoxal-5-phosphate is provided comprising intravenously administering the injectable formulation according to the invention.

[00075] In another aspect, provided is a method of reducing the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of the injectable formulation according to the invention.

[00076] Intravenous administration of pyridoxal-5'-phosphate is particularly useful for treatment of patients undergoing a surgical procedure and requiring antiplatelet and antithrombotic therapies to reduce the frequency of ischemic complications. In a further aspect, provided is a method of treating a patient undergoing a surgical procedure in need of treatment with pyridoxal-5-phosphate comprising intravenously administering the injectable formulation according to the invention. The surgical procedure may be a cardiovascular related procedure such as coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

[00077] An individual dose of the injectable formulation may contain between 10 and 1000 mg of pyridoxal-5'-phosphate, preferably between 50 mg and 100mg, between 100 and 1000 mg of pyridoxal-5'-phosphate and more preferably between 250 and 1000 mg of pyridoxal 5'-phosphate. The injectable formulations according to the invention are suitable for once or twice daily administration, for example such as a single bolus injection. The injectable formulations may also be used for extended or continuous administration.

[00078] The injectable formulations generally are administered in an amount effective for treatment or prophylaxis of a specific indication or indications. It is appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, complicating conditions and the like. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms associated with such disorders.

Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition. For administration to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be 100 to 1000 mg, typically around 200 to 500 mg. The physician in any event may determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[00079] Although the invention has been described with reference to illustrative embodiments, it is to be understood that the invention is not limited to these precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art. All such changes and modifications are intended to be encompassed in the appended claims.

Examples

Example One – Preparation of a Lyophilized Formulation of Pyridoxal 5'-phosphate (P5P)

[00080] Table 1 sets outs the formulation for individual doses of the lyophilized formulation of pyridoxal 5'-phosphate. Each vial provides 250 mg of P5P.

Table 1 - Formulation

Ingredient	Quantity per vial
Sodium Hydroxide	80.5 mg
P5P	250 mg
Mannitol	150 mg
WFI (water for injection)	5.0 ml

[00081] The following procedure is for the preparation of a 5L batch of the lyophilized formulation of pyridoxal 5'-phosphate. The batch size can be scaled up or down by increasing or decreasing the relative amounts proportionately.

[00082] ***Preparation of Glassware and Vials*** - Glass vials were washed and depyrogenated at a temperature of 250 °C ± 15 °C. All glassware and apparatus used in the preparation of the lyophilized formulation including magnetic stir bars, pipettes, Erlenmeyer flasks, flasks, filters, stoppers, and seals, were sterilized by autoclaving at a temperature of 121 °C ± 3 °C for 45 minutes.

[00083] ***Preparation of P5P Solution*** – In calculating the amount of P5P required to make a final concentration of 250mg per vial, a correction factor of 1.08 was used as the water content of the active pharmaceutical ingredient is 7.71%.

[00084] For each 5L batch, 4kg of WFI (80% of total required) was nitrogen flushed in the core of the solution. With magnetic stirring throughout, 80.6 g of sodium hydroxide and 270.4g of P5P were dissolved in the 4kg of WFI to provide a clear solution. The pH of the solution was adjusted accordingly with either 1N NaOH or 1N HCl to a pH of 7.0 to 7.3. Following pH adjustment, 150.3 mg of mannitol was dissolved in the P5P/NaOH solution with continuous magnetic stirring until the solution was clear. Additional WFI was then added to adjust the weight of the solution to 5.245 kg (density 1.049 g/ml). The solution was then sterile filtered through a 0.2 µm Milipack K40 gamma gold model filter and the filter integrity tested.

[00085] ***Lyophilization*** – Individual vials were sterilely filled in a class 100 clean room using a dispensing pump set for dosage volume range of 5.10 – 5.30 mL (equivalent to 5.35 – 5.56 g per vial – by weight). The vials were partially stoppered with bromobuytl stoppers free of 2-mercaptobenzothiazole. Trays of the partially stoppered vials were loaded into lyophilization chambers which had been pre-chilled to 4 °C. Lyophilization was preformed using the following parameters: Cooling temperature: - 45 °C; Primary cooling time - 6 hours;

Primary drying time (in nitrogen atmosphere) - 50 hours; Secondary drying temperature: 35 °C; Secondary drying time - 48 hours.

[00086] After lyophilization, the vials were crimped with aluminum seals having an attached plastic button. The vials were stored at 2 – 8 °C.

Example Two – Comparison of Bioavailability of Intravenously versus Orally Administered Pyridoxal 5'-phosphate (P5P)

[00087] A phase one clinical trial was conducted to compare the pharmacokinetics of intravenously administered P5P and orally administered P5P. The trial was a single dose escalation study.

[00088] For intravenous administration, P5P was administered by bolus injection under fasting conditions. The following doses of P5P were studied: 1, 5, 10, and 20 mg/kg. 6 subjects were assigned to each dosage group.

[00089] For oral administration, P5P was administered as a single non-coated tablet or as a single enteric coated tablet, under fasting conditions. For the non-coated tablets, the following doses of P5P were studied: 5, 10, 17.5, and 25 mg/kg. For the enteric coated tablets, the following doses of P5P were studied: 15, 30 and 60 mg/kg.

[00090] P5P, pyridoxal, and 4-pyridoxic acid were evaluated in both plasma and urine over a 24 hour interval following either intravenous or oral dosing. The results are set out below in Tables 2 and 3.

Table 2 – Pharmacokinetic Parameters for Single Intravenous Dose of P5P

Dose (mg/kg)	Tmax (h)	T½ (h)	Cmax (µg/ml)	AUC-T (µg.h/ml)
1	0.14 ± 0.07	5.11 ± 0.98	19.97 ± 2.95	38.41 ± 4.61
5	0.14 ± 0.07	5.89 ± 0.39	98.82 ± 16.03	172.85 ± 31.95
10	0.10 ± 0.03	5.87 ± 0.89	219.98 ± 9.52	307.97 ± 45.48
20	0.15 ± 0.07	5.03 ± 0.72	424.06 ± 96.88	577.09 ± 62.45

Table 3 - Pharmacokinetic Parameters for Single Oral Dose of P5P

	Dose (mg/kg)	Tmax (h)	T½ (h)	Cmax (µg/ml)	AUC-T (µg.h/ml)
Non-coated tablet	5	9.2 ± 7.7	46 ± 27	0.10 ± 0.03	2.76 ± 1.22
	10	6.6 ± 6.5	47 ± 11	0.10 ± 0.02	3.31 ± 1.22
	17.5	0.5 ± 0.0	54 ± 15	0.27 ± 0.08	2.54 ± 1.06
	25	12.9 ± 5.8	52 ± 32	0.09 ± 0.02	3.93 ± 2.25
Enteric Coated Tablet	15	7.0 ± 2.8	10.0 ± 4.9	2.84 ± 2.99	12.04 ± 10.49
	30	4.3 ± 1.2	20.2 ± 15.6	6.43 ± 12.42	25.80 ± 45.08
	60	4.5 ± 0.5	15.3 ± 6.3	4.47 ± 5.10	18.69 ± 17.83

[00091] The results indicate that the bioavailability of P5P was greater when intravenously administered rather than orally administered.

Example Three - Comparison of Pharmacokineticsand Incidence of Adverse Events for Single Intravenous Doses of 1, 5, 10, and 20 mg/kg of Pyridoxal 5'-phosphate (P5P)

[00092] **Methodology** - This was a single-blind, single-dose escalation, non-randomized, 4-phase, non-crossover study designed to evaluate the safety and tolerability of P5P intravenous injectable solution at doses of 1, 5, 10, 20 mg/kg, administered to four groups of healthy male and female subjects under fasting conditions and to estimate pharmacokinetic parameters of P5P.

[00093] Subjects were assigned to one of the four groups (six subjects per group) under fasting conditions.

[00094] Concentrations of pyridoxal-5'-phosphate (P5P) were measured from the plasma samples collected over a 24-bour interval after dosing in each phase.

[00095] Pharmacokinetic parameters: AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el},T_{half}, V_d, CL, MRT and F were estimated based on pyridoxal-5'-phosphate (P5P) plasma levels for each subject that was in the final data set.

[00096] Safety data were collected for each subject throughout the study by recording vital signs, ECGs and reported adverse events.

Number of subjects (planned and analyzed)

[00097] Six (6) subjects were dosed in Group 1 (1 mg/kg). Six (6) subjects completed phase I of the study and were analyzed.

[00098] Six (6) subjects were dosed in Group 2 (5 mg/kg). Six (6) subjects completed phase 2 of the study and were analyzed.

[00099] Six (6) subjects were dosed in Group 3 (10 mg/kg). Six (6) subjects completed phase 3 of the study and were analyzed.

[000100] Six (6) subjects were dosed in Group 4 (20 mg/kg). Five (5) subjects completed phase 4 of the study and were analyzed.

[000101] Diagnosis and Main Criteria for Inclusion

[000102] Subjects met all of the following inclusion criteria within 21 days prior to drug administration.

[000103] 1) Healthy, non-smoking, male and female subjects, 18 to 55 years of age (inclusive).

[000104] 2) Body weight within ± 10% of the appropriate weight for the subject's height and frame (as published in the 1983 Metropolitan Life Insurance Company Scale, Statistical Bureau).

[000105] 3) Negative for: HIV; Hepatitis B surface antigen and Hepatitis C antibody; Urine tests for drugs of abuse (marijuana, amphetamines, barbiturates, cocaine, opiates. benzodiazepines and methadone); Cotinine (urine test); Serum HCG (females only)

[000106] 4) No significant diseases or clinically significant findings in a physical examination.

[000107] 5) No clinically significant abnormal laboratory values.

[000108] 6) No clinically significant findings in vital signs measurements and a 12-lead electrocardiogram (ECG).

[000109] 7) Be informed of the nature of the study and given written consent prior to receiving any study procedure.

[000110] 8) Females who participate in this study are: unable to have children (e.g. post-menopausal, tubal ligation, hysterectomy) OR willing to remain abstinent [not engage in sexual intercourse] OR willing to use an effective method of double-barrier birth control [partner using condom and female using diaphragm, contraceptive sponge, spermicide or IUD] OR willing to use a hormonal contraceptive [oral, inserted under the skin, patch or injection].

[000111] 9) Females who participate in this study are non-lactating.

[000112] The test product used was a P5P Intravenous Injectable Solution, 50mg/ml, which was prepared in accordance with the methods of Example 1 (CanAm BioResearch Inc, Canada); Lot No.: LP1459: Manufacturing Date: 12/03. A single 1, 5, 10 or 20 mg/kg dose was given by intravenous injection. The duration of treatment was a single dose.

Criteria for Evaluation

[000113] **Primary Endpoint - Safety Parameters** - The safety parameters investigated in this study were vital signs measurements (blood pressure, pulse rate), ECG measurements (1, 2 and 12 hours post-dose), platelet function testing, and severity and causality of adverse events experienced by subjects during the study period and laboratory assessments (clinical chemistry, hematology, urinalysis).

[000114] Secondary Endpoint - Pharmacokinetic (PK) Parameters - Plasma concentrations of pyridoxal-5'-phosphate (P5P) were measured by a validated analytical method. Based on these concentration levels, AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, T_{half}, V_d, CL, MRT and F were estimated.

[000115] Statistical Methods - Descriptive statistics were calculated by treatments for the estimated pharmacokinetic parameters.

Discussion and Conclusions

[000116] Overall the safety profile of P5P injectable solution established in this clinical study demonstrates that the product is well tolerated with no serious or lasting treatment related effects at doses up to 20 mg/kg, when administered as a single dose. Common side effects of P5P observed in this study include nausea, vomiting and stomach upset. None of the adverse events had a significant impact on the safety of the subjects or integrity of the study results.

[000117] Based on the adverse event profile generated from the results of this study, P5P is safe and well tolerated in doses up to 20 mg/kg.

[000118] The P5P pre-dose concentrations were very low, less than 1% of the corresponding C_{max} values (range: 0.01% to 0.44%). The pyridxoal (PAL) pre-dose concentrations were slightly larger, between 0.06% and 2.47% of the Cmax values.

[000119] Only one subject (Subject 23) exhibited a non-zero pre-dose level for 4-pyridoxic acid (PA) and it represented 0.06% of the C_{max} parameter. Note that where applicable, the baseline (mean value of the pre-dose levels) were subtracted from the measured analyte levels before the pharmacokinetic analysis of the data.

[000120] The P5P concentration-time profiles after the initial rapid increase exhibited a moderate decrease, attributable mainly to a distribution phase followed by a slower elimination phase (Figures 1 to 3). Only 3 data-points were considered on the terminal linear phase and used for the estimation of the

apparent elimination half-life. It is possible that the 24-hour sampling interval was not long enough to capture the real elimination phase of P5P. The estimated values were consistent over all doses, between 5 and 6 hours (Table 4).

Table 4 - Plasma Pharmacokinetic Parameters for P5P

Plasma Pharmacokinetic Parameters for Pyridoxal-5'-Phospbate (P5P) Mean (CV%)					
Group		1	2	3	4
Dose of P5P		1 mg/kg	5 mg/kg	10 mg/kg	10 mg/kg
No. of subjects		6	6	6	5
AUC(O-t)	(µ.g*'h/mL)	38.413 (12)	172.849 (18)	301.913 (15)	577.091 (11)
AUC(o-inf)	(µ.g*h/mL)	39.116(13)	175.910 (19)	312.439 (15)	584.564 (11)
Cmax	(µg/mL)	19.968 (15)	98.823 (16)	219.930 (4)	424.058 (23)
Tmax	(h)	0.14(49)	0.14 (49)	0.10 (35)	0.15 (47)
Kel	(1/h)	0.1399 (10)	0.1180 (7)	0.1205 (16)	0.1400 (15)
T1/2	(h)	5.11 (19)	5.89 (1)	5.81 (15)	5.03 (14)
MRT	(h)	3.73 (27)	3.52 (12)	3.11 (12)	3.32 (11)
CL	(mL/h)	1759(16)	1928 (23)	21110 (24)	2385 (18)
Vd	(mL)	12959 (22)	16336 (22)	18002 (13)	17543 (30)

[000121] The distribution dominated phase was not clearly observable for the two metabolites, pyridoxal (PAL) and 4-pyridoxic acid (PA). The apparent elimination half-life was approximately 4 hours for PAL (Table 5) and approximately 2 to 3.5 hours for PA (Table 6).

Table 5 - Plasma Pharmacokinetic Parameters for PAL

Plasma Pharmacokinetic Parameters for Pyridoxal (PAL) Mean (CV%.)					
Group		1	2	3	4
Dose of P5P		1 mg/kg	5 mg/kg	10 mg/kg:	20 mg/kg
No. of subjects		6	6	6	5
AUC (0-t)	(µ*g.h/mL)	2.020 (34)	10.132 (13)	39.143 (16)	94.403 (20)
AUC (0-inf)	(µg*h/lmL)	2.070 (32)	10.365 (14)	39.488 (16)	95.185 (20)
Cmax	(µ/lmL)	0.591 (26)	2.480 (18)	13.267 (23)	25.902 (13)
Tmax	(h)	0.46 (54)	0.71 (92)	0.42 (36)	0.32 (29)
Kel	(1/h)	0.1980 (37)	0.1797 (30)	0.1666 (11)	0.1770 (18)
T1/2	(h)	3.96 (40)	4.25 (39)	4.20 (11)	4.01 (16)
MRT	(h)	3.70 (16)	4.40 (19)	3.68 (13)	3.98 (8)

Table 6 - Plasma Pharmacokinetic Parameters for PA

Plasma Pharmacokinetic Parameters for 4-Pyridoxic Acid (PA)					
		Mean (CV%)			
Group		1	2	3	4
Dose of P5P		1 mg/kg	5 mg/kg:	10 mg/kg	20 mg/kg
No. of subjects		6	6	6	5
AUC(0-t)	(µg*h/mL)	1.504 (55)	10.482 (14)	22.666 (16)	51.901 (23)
AUC(0-inf)	(µg*h/mL)	1.993 (34)	10.749 (14)	22.982 (1 5)	53.021 (14)
Cmax	(µg/mL))	0.419 (32)	2.447 (15)	5.361 (27)	16.065 (21)
Tmax	(h)	1.04 (24)	0.71 (23)	0.74 (53)	0.73(51)
Kel	(1/h)	0.311 (53)	0.3315 (13)	0.2676 (24)	0.2158(32)
T1/2	(h)	2.82 (52)	2.12 (13)	2.73 (21)	3.48 (31)
MRT	(h)	4.50 (45)	3.48 (8)	3.85 (7)	4.13 (15)

[000122] PAL reached maximum plasma levels at approximately 0.30 to 0.70 hours (Figures 4 to 6), while PA attained maximum concentrations at approximately 0.70 to 1.0 hours (Figures 7 to 9), after the beginning of the iv. infusion. These values are consistent with the sequential formation of these metabolites.

[000123] The urinary excretion of the unchanged P5P is negligible. Less than 0.5% of the administered dose was found as P5P in the urine (Table 10). Similarly, very little of the dose was excreted in urine as PAL, between approximately 2 to 3% of the total dose (Table 10).

[000124] PA represented the largest amounts found in urine. Over a 24-hour interval, between 30% and 52% of the given dose was excreted in urine as 4-pyridoxic acid.

[000125] The results of the analysis of the relationship between the values of pharmacokinetic parameters and dose are summarized in the Table 7 below.

Table 7 - Summary of Urinary Excretion

Cumulative Urinary Excretion as Percent of the Dose Percent (CV%)				
Group	1	2	3	4
Dose of P5P	1 mg/lkg	5 mg/kg	10 mg/kg	20 mg/kg
No. of subjects	6	6	6	5
P5P	0.06 (161)	0.08 (96)	0.02 (167)	0.26(73)
PAL	1.93 (101)	3.00 (37)	2.73 (20)	2.46 (33)
PA	52.25 (28)	47.18(32)	29.78 (32)	40.55 (54)
Total	54.24 (27)	50.26(30)	32.53 (30)	43.27 (52)

Table 8 - Summary of Pharmacokinetic Parameters versus Dose Relationship Equation

Summary of PK Parameters versus Dose Relationship Equation: ln(pK Parameter) = b0+ bl * ln (Dose)						
Parameter	Intercept (bo)	Coef. for Dose (b1)	95% Lower Limit (b1)	95% Upper Limit (b1)	Significance of bl	R^2
P5P						
lnAUCi	3.67	0.90	0.85	0.96	<0.0001	0.98107
lnCmax	2.98	1.03	0.97	1.08	<0.0001	0.98411
lnCl	7.44	0.10	0.02	0.17	0.0128	0.26048
lnThalf	1.67	0.02	-0.05	0.08	0.6177	0.01207
lnMRT	1.29	-0.05	-0.11	0.02	0.1568	0.09314
PAL						
lnAUCi	0.56	1.30	1.18	1.41	<0.0001	0.96365
lnCmax	-0.72	1.30	1.16	1.45	<0.0001	0.94194
lnThalf	1.33	0.03	0.08	0.14	0.5604	0.01640
lnMRT	1.33	0.02	-0.05	0.08	0.5671	0.01585
PA						
lnAUCi	0.62	1.10	1.01	1.18	<0.0001	0.97052
lnCmax	-0.98	1.20	1.09	1.31	<0.0001	0.96098
lnThalf	0.82	0.08	-.006	0.22	0.2604	0.0599
lnMRT	1.37	-0.01	-0.11	0.09	0.7995	0.00314

[000126] Both plasma AUC_{inf} and C_{max} parameters are dose-dependent for all analytes. The coefficient of determination (R^2) for the linear regression is quite high and the estimated coefficient for the dose (b1) is significantly different from zero.

[000127] The dose-proportionality is clearly demonstrated for plasma P5P C_{max} parameter since the 95% confidence interval (CI) of b1 contains 1. In the case of plasma AUC_{inf} of P5P appears to be a slight deviation from proportionality. The 95% CI for b1, 0.85-0.96, does not contain the value of 1. However, the deviation seems quite small and it may be explained by the experimental error. This deviation may be the reason for the dose dependency observed for the clearance, CL. The b1 coefficient is significantly different from zero but the coefficient of determination is very low, 0.26048, and the value of b1 is very low as well, 0.10.

[000128] In the case of the metabolites, PAL and PA, both parameters, AUC_{inf} and C_{max}, seem to increase more than expected based on dose. The 95% confidence intervals for the b1 coefficient lay above the value of 1. This deviation is more pronounced for the PAL analyte.

[000129] The apparent elimination half-life (T_{half}) and the mean residence time (MRT) are independent of the dose for all 3 analytes. The coefficient of the dose (b1) is not significantly different from zero, therefore it may be concluded that the elimination half-life and the mean residence time are constant over the 1 mg/kg to 20 mg/kg dose range.

Example Four - Bioavailability and Incidence of Adverse Events for Single Intravenous Dose of 10 mg/kg of Pyridoxal 5'-phosphate (P5P) Over 4 Day Period

[000130] **Data sets analyzed** - Six (6) healthy, adult non-smokers were administered intravenously a single daily dose of 10 mg/kb of P5P for four consecutive days and completed the study. In accordance with the study protocol, data from all subjects who completed the study were used for pharmacokinetic and statistical analysis.

[000131] **Demographics** - Age (years): mean = 33 ± 10; range = 19-49; median = 32. Height (cm): mean = 168.7 ± 4.8; range = 163.0-175.5; median

= 68.75. Weight (kg): mean = 70.9 ± 10.0; range =56-0-83.2; median = 68.75. BMI (kg/m^2): mean = 24.9 ± 3.0; range = 20.6-29.3; median = 25.

[000132] Analytical Methods - Plasma and urine samples were used for analysis. P5P, PAL, and PA levels were determined by HPLC/FLD. The quantitation level was 5ng/mL for plasma and 100 ng/mL for urine. The sample analysis calibration curve range was 5 ng/mL to 5000 ng/mL for plasma and 100 ng/mL to 50,000 ng/mL for urine.

[000133] Safety Methods - The safety parameters investigated in this study were: adverse events, vital sign measurements, ECGs, physical examination and standard laboratory evaluations.

Measurements of Treatment Compliance

[000134] Measurements of treatment compliance were 100% as subjects were dosed under direct observation; subject identification was verified and cross-checked with the pre-dispensed medication. In addition, subjects were confined to the SFBC Anapharm Clinical Research Facility from at least 10 hours prior to placebo injection, on Day 0 until after the 24.0-hour post 4th dose blood draw on Day 5.

Statistical Methods

[000135] The P5P, PAL and PA plasma concentration data for each subject, sampling time and treatment day were electronically transferred from BRI Biopharmaceutical Research Inc. to the statistical division of SFBC An.apbam1. The data were cross-checked against the hard copies.

[000136] Time deviations during sampling were treated as follows: for all sampling times, the difference between the scheduled and the actual sampling time was considered acceptable if it was inferior to 1 minute. When the difference exceeded this time limit, the actual sampling times (rounded off to three decimal digits) were used to calculate pharmacokinetic parameters except for pre-dose samples, which were always reported as zero (0.000), regardless of

time deviations. Scheduled sampling times are presented in concentration tables and graphs of the statistical section of the report.

[000137] Samples that were not available were recorded as NS (No sample) in the concentration tables. These samples were treated as missing for pharmacokinetic and statistical analyses.

[000138] Pharmacokinetic analyses (non-compartmental and compartmental) were performed at SFBC Anapharm. Pharmacokinetic parameters were calculated using either Bioequiv (release 3.40) or WinNonLinTM (release 4.0.1). Bioequiv is proprietary software developed and tested for bioequivalence studies at SFBC Anapharm. This software performs non-compartmental ana1yses of pharmacokinetic parameters and statistical analyses (via SAS release 6.12) according to FDA, HPFB and BMEA guidance.

[000139] The mean, standard deviation (SD), coefficient of variation (CV (%)) and range (min. and max.) were calculated for plasma concentrations of P5P (both baseline corrected and uncorrected), PAL and PA for each sampling time and treatment.

[000140] For the non-compartmental pharmacokinetic analyses the mean. SD, CV (%). range (min. and max.), median and interquartile range were calculated for the AUC_{0-t}, (ng·h/mL), $AUC_{0-\tau}$ (ng·h/mL), AUC_{0-inf} (ng·h/mL), C_{max} (ng/mL), C_{min} (ng/mL), C_{avg} (ng/mL), Fl(%), Ae_{0-t} (ng), $AUC_{t/inf}$ (%), T_{max} (h), $T_{½\ el}$ (h), K_{el} (h^{-1}), TLIN (h), LQCT (h). CL_T (L/h), CL_R (L/h). V_β (L), MRT (h) and Accumulation ratio. The calculation of these pharmacokinetic parameters is explained below.

Maximum observed concentration, minimum observed concentration, average concentration and time of observed peak concentration

[000141] C_{max} the maximum observed concentration, and T_{max}, the time to reach that peak concentration, were determined for each subject and for each analyte. For Day 4 data, C_{min} the minimum observed concentration was

determined for each subject and for each analyte and C_{avg} was calculated as $AUC_{0-\tau}/\tau$.

[000142] Percentage of Fluctuation - For Day 4 data, the peak-through percentage of fluctuation over one dosing interval (FI(%)) was calculated as: $100 * ([C_{max}-C_{min}]/C_{avg})$

[000143] Half-Life and Elimination Rate Constant - To calculate the elimination rate constant (K_{el}), regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (TLIN) and the time at which the last concentration above the limit of quantification (LQCT) occurred. The K_{el} was taken as the slope multiplied by (-1) and the apparent half-life ($T_{1/2\ el}$) as $(\ln 2)/K_{el}$.

[000144] TLIN and LQCT - TLIN, the time point where ln-linear K_{el} calculation begins, and LQCT, the sampling time of the last quantifiable concentration used to estimate the K_{el} were determined by the scientist (according to SFBC Anapharm's standard operating procedures) for each subject and for each treatment. At least 4 non-zero observations during the terminal elimination phase were used to calculate the K_{el}. A minimum of 3 observations were used if less than 4 observations were available.

[000145] Areas Under the Concentration-Time Curves - AUC_{0-t} was calculated using the linear trapezoidal rule from time 0.000 h until the last non-zero concentration.

[000146] $AUC_{0-\tau}$ was calculated using the linear trapezoidal rule from time 0.000 h until 24.0 h.

[000147] The AUC_{0-inf} was calculated as:

$$AUC_{0-t} + C_t/K_{el}$$

Where: C_t = the last observed non-zero concentration for that treatment, AUC_{0-t} = the AUC from time zero to the time of the last non-zero concentration for that analyte and K_{el} = the elimination rate constant.

[000148] $AUC_{t/inf}$ was calculated as the ratio of AUC_{o-t} (or $AUC_{0-\tau}$) to AUC_{0-inf}.

[000149] **Total and Renal Clearance -** Total body clearance was estimated for P5P and was calculated as $Dose/AUC_{0-inf}$. Renal clearance was estimated for all analytes and was calculated as Ae_{0-t}/AUC_{0-inf} where Ae_{0-t} is the cumulative urinary excretion from 0.000 h until 24.0 h.

[000150] **Volume of Distribution -** Volume of distribution based on the terminal phase (Vβ) was calculated as $Dose/(K_{el} * AUC_{0-inf})$ for P5P and as $Ae_{0-t}/(K_{el} * AUC_{0-inf})$ for PAL and P A. For Day 4 data. AUC o-τ was used instead of AUC_{0-inf}.

[000151] **Mean Residence Time -** The mean residence time was calculated as $AUMC/AUC_{0-inf}$.

[000152] **Accumulation Ratio -** For Day 4 data, the theoretical accumulation ratio (using the studied dosing interval and assuming dose-linear kinetics) was calculated as $1/[1-e^{(-kel*\tau)}]$.

[000153] **Statistical Analysis -** For all analytes, analysis of variance was performed on the ln transformed data of AUC_{0-t}, AUC_{0-inf} and C_{max}. All ANOVAs were performed with the SAS (release 6.12 for Windows) General Linear Models Procedure (GLM). The model included subject and treatment day. All sums of squares (Types I, II, III, and IV) were reported. The subject and day effects were tested against the residual mean square error. Probability (P) values were derived from Type III sums of squares. For all analyses, effects were considered statistically significant if the probability associated with "F" less than 0.050. Based on pairwise comparisons of the ln-transformed of AUC_{0-t}, AUC_{0-inf} and C_{max} data, the ratios of the least squares means, calculated according to the formula "$e^{(X-Y)}$ X 100", as well as the 90% geometric confidence intervals for ln-

transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were determined. Finally, the intrasubject CVs were also determined.

Analysis of Pharmacokinetics and Statistical Issues

Non-Compartmental Pharmacokinetic Analysis

[000154] The primary non-compartmental pharmacokinetic parameters for this study were: AUC_{0-t}, AUC_{0-inf}, and C_{max} and the secondary pharmacokinetic parameters were $AUC_{t/inf}$, T_{max}, K_{el}, $T_{1/2\ el}$, CL_T (for P5P), CL_R, V_β, MRT, and Ae_{0-t}. The following parameters were also calculated for Day 4 data: C_{min}, C_{avg}, Fl(%), $AUC_{0-\tau}$, and Accumulation ratio.

[000155] Blood sampling for pharmacokinetic analysis on Days 1 and 4 were collected at pre-dose and 0.083, 0.167. 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.0, and 24.0 hours post-dose on each day. Urine samples were collected at 8 time intervals: at 0.000-4.00, 4.00-8.00, 8.00-12.0, and 12.0-24.0 hours post-dose on Days 1 and 4.

[000156] The plasma concentrations measured for each subject at each sampling time appear in Tables 9 and 10 for baseline corrected P5P, in Tables 11 and 12 for uncorrected P5P, in Tables 13 and 14 for PAL and in Tables 14 and 15 for PA according to treatment day. The plots of the mean plasma levels over the sampling period are presented for both untransformed and ln-transformed in Figures 10-11 for baseline corrected P5P, in Figures 12-13 for uncorrected P5P, in Figures 14-15 for PAL and in Figures 16-17 for P A. The lines in ln-transformed data figures represent the regression lines used to estimate the K_{el}.

Table 9 - Summary of Pharmacokinetic Parameters for P5P (Corrected)

Parameters		P5P (Day 1) (A) Mean	±	SD	CV(%)	P5P (Day 4) (B) Mean	±	SD	CV (%)
AUC_{0-t}	(ng.h/mL)	277978.56	±	54823.24	19.72	302742.00	±.	85962.45	28.39
$AUC_{0-\tau}$	(ng.h/mL)	-		-	.	302742.00	±	85962.45	28.39
AUC_{0-inf}	(ng.h/mL)	283108.04	±	58590.23	20.70	311164.84	±	90706.89	29.09
$AUC_{t/inf}$	(%)	98.33	±	0.95	0.96	97.23	±	1.02	1.05
C_{max}	(ng/mL)	190536	±	27999	14.69	213392	±	46782	21.92
C_{min}	(ng/mL)	-		-	-	946	±	582	61.50
C_{avg}	(ng/mL)	-		-	-	12614.42	±	3582.24	28.40
Fl(%)	(%)	-		.	-	1734.69	±	378.44	21.82
T_{max}	(h)	0.089	±:	0.040	45.25	0.081	±	0.034	41.92
T_{max}	(h)	0.067	±	0.025	-	0.067	±	0.000'	-
K_{el}	(h^{-1})	0.1381	±	0.0226	16.38	0.1183	±	0.0170	14.41
$T_{1/2\ el}$	(h)	5.14	±	0.91	17.65	5.96	±	0.85	14.33
CL_{τ}	(L/h)	2.55	±	0.38	14.75	2.42	±	0.38	15.82
V_{β}	(L)	18.59	±	1.87	10.05	20.75	±	4.08	19.65
MRT	(h)	3.40	±	0.70	20.68	3.99	±	0.67	16.84
Accumulation Ratio		-		-	-	1.07	±	0.03	2.62

Table 10 - Summary of Non-Compartmental Pharmacokinetic Parameters for P5P (Corrected)

P5P (Day 4) (B) vs P5P (Day 1) (A)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio [1]	107.31%	108.53%	110.71%
90 % Geometric C.I.[2]	98.28% to 117.16%	99.88%10117.91%	98.76% to 124.10%
Intra-Subject CV	7.56%	7.14%	9.84%

[1] Calculated using least-squares means according to the formula: $e^{(P5P\ (Day\ 4)\ (B)-P5P(Day\ 1)\ (A))}X100$

[2] 90% Geometric Confidence Interval using ln-transformed data

Table 11 - Summary of Pharmacokinetic Parameters for P5P (Uncorrected)

Parameters		P5P (Day 1) (A) Mean	±	SD	CV(%)	P5P (Day 4) (B) Mean	±	SD	CV (%)
AUC_{0-t}	(ng.h/mL)	278624.79	±	55320.00	19.85	303392.72	±	86509.09	28.51
$AUC_{0-\tau}$	(ng.h/mL)	-		-	-	303393.72	±	86509.09	28.51
AUC_{0-inf}	(ng.h/mL)	284071.57	±	59408.49	20.91	312753.76	±	91554.52	29.27
$AUC_{t/inf}$	(%)	98.24	±	1.01	1.03	97.14	±	1.04	1.07
C_{max}	(ng/mL)	190564	±	27998	14.69	213419	±	46789	21.92
C_{min}	(ng/mL)	-		-	-	974	±	603	61.89
C_{avg}	(ng/mL)	-		-	-	12641.59	±	3605.03	28.52
FI(%)	(%)	848625	±	612120	72.13	1731.62	±	378.85	21.88
T_{max}	(h)	0.089	±	0.040	45.25	558650	±	414503	74.20
T_{max}	(h)	0.067	±	0.025	-	0.081	±	0.034	41.92
K_{el}	(h^{-1})	0.1360	±	0.0226	16.60	0.067	±	0.000	-
$T_{1/2\ el}$	(h)	5.22	±	0.94	18.00	0.1170	±	0.0168	14.35
CL_{τ}	(L/h)	2.55	±	0.38	14.92	6.02	±	0.85	14.14
V_{β}	(L)	0.00279	±	0.00177	63.53	2.42	±	0.38	15.92
MRT	(h)	18.82	±	1.89	10.03	0.00174	±	0.0078	44.71
Accumulation Ratio .		3.45	±	0.73	21.20	20.92	±	4.05	19.36
		-		-	-	4.03	±	0.68	16.93
						1.07	±	0.03	2.63

Table 12 - Summary of Non-Compartmental Pharmacokinetic Parameters for P5P (Uncorrected)

P5P (Day 4) (B) vs P5P (Day 1) (A)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	107.28%	108.50%	110.70%
90 % Geometric C.I.[2]	98.28% to 117.11%	99.90% to 117.83%	98.76% to 124.10%
Intra-Subject CV	7.54%	7.10%	9.84%

[1] Calculated using least-squares means according to the formula: $e^{(P5P\ (Day\ 4)\ (B)-P5P(Day\ 1)\ (A))}X100$

[2] 90% Geometric Confidence Interval using In-transformed data

Table 13 - Summary of Pharmacokinetic Parameters for PAL

Parameters		PAL (Day 1) (A) Mean	±	SD	CV(%)	PAL (Day 4) (B) Mean	±	SD	CV (%)
AUC_{0-t}	(ng.h/mL)	22292.93	±	3412.91	15.31	29682.94	±	5021.44	16.92
$AUC_{0-\tau}$	(ng.h/mL)	-		-	-	29682.94	±	5021.44	16.92
AUC_{0-inf}	(ng.h/mL)	22444.06	±	3396.70	15.13	30077.45	±	5010.46	16.66
$AUC_{t/inf}$	(%)	99.31	±	0.41	0.41	98.66	±	0.87	0.89
C_{max}	(ng/mL)	7629	±	6075	79.63	6902	±	2936	42.54
C_{min}	(ng/mL)	-	-	-	-	56.8	±	28.3	49.95
C_{avg}	(ng/mL)	-	-	-	-	1236.81	±	209.24	16.92
Fl(%)	(%)	-	-	-	-	537.81	±	151.79	28.22
T_{max}	(h)	18583712	±	6900473	37.13	21011635	±	4491980	21.38
T_{max}	(h)	0.525	±	0.102	19.45	0.691	±	0.188	27.22
K_{el}	(h^{-1})	0.483	±	0.000	-	0.733	±	0.188	-
$T_{1/2\ el}$	(h)	0.2064	±	0.0262	12.70	0.1775	±	0.0236	13.27
CL_{τ}	(L/h)	3.40	±	0.41	12.11	3.96	±	0.54	13.56
V_{β}	(L)	0.85952	±	0.37133	43.20	0.72392	±	0.19711	27.23
MRT	(h)	4.35	±	2.18	50.05	4.21	±	1.63	38.82
Accumulation Ratio		4.06	±	0.70	17.24	4.74	±	0.96	20.29
		-		-	-	1.02	±	0.01	0.91

Table 14 - Summary of Non-Compartmental Pharmacokinetic Parameters for PAL

PAL (Day 4) (B) vs PAL (Day 1) (A)			
	AUC_{0-t}	AUC_{0-inf}	
Ratio[1]	132.83%	133.70%	101.45%
90 % Geometric C.I.[2]	128.10% to 137.73%	128.85% to 138.74%	79.57% to 129.33%
Intra-Subject CV	3.12%	3.18%	21.10%

[1] Calculated using least-squares means according to the formula: $e^{(PAL\ (Day\ 4)\ (B)-PAL(Day\ 1)\ (A))}X100$

[2] 90% Geometric Confidence Interval using ln-transformed data

Table 15 - Summary of Pharmacokinetic Parameters for PA

Parameters		PA (Day 1) (A) Mean	±	SD	CV(%)	PA (Day 4) (B) Mean	±	SD	CV (%)
AUC_{0-t}	(ng.h/mL)	20736.28	±	3586.19	17.29	20704.80	±	3714.71	17.94
$AUC_{0-\tau}$	(ng.h/mL)	-		-	-	21240.85	±	3451.14	16.25
AUC_{0-inf}	(ng.h/mL)	21219.58	±	3686.62	17.37	21097.95	±	3614.47	17.13
$AUC_{t/inf}$	(%)	97.73	±	1.21	1.24	98.01	±	1.42	1.45
C_{max}	(ng/mL)	4362	±	797	18.27	4238	±	771	18.20
C_{min}	(ng/mL)	-		-	-	12.9	±	25.1	194.30
C_{avg}	(ng/mL)	-		-	-	885.04	±	143.80	16.25
Fl(%)	(%)	-		-	-	482.53	±	82.29	17.05
T_{max}	(h)	172950596	±	66502786	38.45	225885311	±	47312304	20.95
T_{max}	(h)	0.611	±	0.215	35.24	0.528	±	0.101	19.13
K_{el}	(h^{-1})	0.483	±	0.188	-	0.483	±	0.013	-
$T_{1/2\ el}$	(h)	0.3092	±	0.0526	17.01	0.2547	±	0.0524	20.59
CL_{τ}	(L/h)	2.30	±	0.45	19.38	2.83	±	0.67	23.55
V_{β}	(L)	8.61246	±	4.23700	49.20	10.75339	±	2.18960	20.36
MRT	(h)	28.61	±	14.16	49.49	44.45	±	14.95	33.63
		3.85	±	0.61	15.94	4.24	±	0.92	21.69
Accumulation Ratio		-		-	-	1.00	±	0.01	0.58

Table 16 - Summary of Non-Compartmental Pharmacokinetic Parameters for PA

PA (Day 4) (B) vs PA (Day 1) (A)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	99.75%	99.47%	97.17%
90 % Geometric C.I.[2]	95.89% to 103.76%	94.73% to 104.46%	94.16% to 100.28%
Intra-Subject CV	3.39%	4.20%	2.71%

[1] Calculated using least-squares means according to the formula: $e^{(PA\ (Day\ 4)\ (B)-PA(Day\ 1)\ (A))}X100$
[2] 90% Geometric Confidence Interval using ln-transformed data

[000157] Calculated non-compartmental pharmacokinetic parameters for each subject according to treatment day are shown in Tables 10, 12, 14, and 16 for corrected and uncorrected P5P, PAL, and PA.

Primary Parameters

[000158] Area under the concentration-time curve (0-t hours) was calculated for each subject and analyte. The P5P (baseline corrected) results are presented in Tables 9 and 10. Mean values (%CV) for AUC_{0-t} were 277978.56 ng·h/mL (19.72%) for Day 1 and 302742.00 ng·h/mL (28.39%) for Day 4. The P5P (uncorrected) results are presented in Tables 11 and 12. Mean values (%CV) for AUC_{0-t} were 278624.79 ng·h/mL (19.85%) for Day 1 and 303393.72 ng·h/mL (28.51%) for Day 4. The PAL results are presented in Tables 11 and 12. Mean values (%CV) for AUC_{0-t} were 22292.93 ng·h/mL (15.31%) for Day 1 and 29682.94 ng·h/mL (16.92%) for Day 4. The PA results are presented in Tables 11 and 12. Mean values (%CV) for AUC_{0-t} were 20736.28 ng·h/mL (17.29%) for Day 1 and 20704.80 ng·h/mL (17.94%) for Day 4. The ANOVA performed on the ln-transformed AUC_{0-t} data are presented in Tables 710, 12, 14, and 16 for P5P (baseline corrected), P5P (uncorrected), PAL and PA, respectively. ANOVA did not detect any statistically significant difference between Day 4 and Day 1 for this parameter for P5P (baseline corrected and uncorrected) and PA. ANOVA detected a statistically significant difference between Day 4 and Day 1 for this parameter for PAL. The least-squares means ratios, the 90% geometric confidence intervals and intra-subject CVs were also determined for P5P (baseline corrected), P5P (uncorrected), PAL and P A, respectively. These results are summarized on Table 17.

Table 17 - Summary of least-squares means ratios, 90% geometric confidence intervals and intra-subject CVs for AUC_{0-t}

AUC_{0-t}	Treatment Day 4 (B) *vs* Treatment Day 1 (A)			
	P5P Baseline corrected	P5P Uncorrected	PAL	PA
Ratio of LS Means	107.31%	107.28%	132.83%	99.75%
90% Geometric C.I.	98.28% to 117.16%	98.28% to 117.11%	12&.lO% to 137.73%	95.89% to 103.76%
Inter-Subject CV	7.56%	754%	3.12%	3.39%

Area under the concentration-time curve (0-infinity) was calculated for each subject and analyte. The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for AUC_{0-inf} were 283108.04 ng·h/mL (20.70%) for Day 1 and 311764.84 ng·h/mL (29.09%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for AUC_{0-inf} were 284071.57 ng·h/mL (20.91%) for Day 1 and 312753.76 ng·h/mL (29.27%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for AUC_{0-inf} were 22444.06 ng·h/mL (15.l3%) for Day 1 and 30077.45 ng·h/mL (16.66%) for Day 4. The PA results are presented in Table 15. Mean yalues (%CV) for AUC_{0-inf} were 21219.58 ng·h/mL (17.37%) for Day 1 and 21097.95 ng·h/mL (17.13%) for Day 4.

[000159] ANOVA did not detect any statistically significant difference between Day 4 and Day 1 for this parameter for P5P (baseline corrected and uncorrected) and PA. ANOVA detected a statistically significant difference between Day 4 and Day 1 for this parameter for PAL. The least-squares means ratios, the 90% geometric confidence intervals and intra-subject CVs were also determined for

P5P (baseline corrected), P5P (uncorrected), PAL and PA, respectively. These results are summarized on Table 18.

Table 18 - Summary of least-squares means ratios, 90% geometric confidence intervals and intra-subject CVs for AUC $_{0\text{-inf}}$

AUC $_{0\text{-inf}}$	Treatment Day 4 (B) *vs* Treatment Day 1 (A)			
	P5P Baseline corrected	P5P Uncorrected	PAL	PA
Ratio of LS Means	108.53%	108.50%	133.70%	99.47%
90% Geometric C.I.	99.88% to 117.91 %	99,90% to 117.83%	128.85% to 138.74%	94.73% to 104.46%
Intra-Subject CV	7.14%	7.10%	3.18%	4.20%

[000160] The peak or maximal plasma concentration was calculated for each subject and analyte. The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for C_{max} were 190536 ng/mL (14.69%) for Day 1 and 213392 ng/mL (21.92%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for C_{max} were 190564 ng/mL (14.69%) for Day 1 and 213419 ng/mL (21.92%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for C_{max} were 7629 ng/mL (79.63%) for Day 1 and 6902 ng/mL (42.54%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for C_{max} were 4362 ng/mL (18.27%) for Day 1 and 4238 ng/mL (18.20%) for Day 4. ANOVA did not detect any statistically significant difference between treatments for this parameter for all analytes. The least-squares means ratios, the 90% geometric confidence intervals and intra-subject CVs were also determined for P5P (baseline corrected), P5P (uncorrected), PAL and PA, respectively. These results are summarized on Table 19.

Table 19 - Summary of least-squares means ratios, 90% geometric confidence intervals and intra-subject CVs for C_{max}

C_{max}	Treatment Day 4 (B) *vs* Treatment Day 1 (A)			
	P5P Baseline corrected	P5P Uncorrected	PAL	PA
Ratio of LS Means	110.71%	110.70%	101.45%	97.17%
90% Geometric C.I.	98.76% to 124.10%	98.76% to 124.10%	79.57% to 129.33%	94.16% to 100.28%
Intra-Subject CV	9.84%	9.84%	21.10%	2.71%

Secondary parameters common to Day 1 and Day 4

[000161] The ratio of AUC_{0-t} to AUC_{0-inf} (%) was calculated for each subject and for each analyte. The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for $AUC_{t/inf}$ were 98.33% (0.96%) for Day 1 and 97.23% (1.05%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for $AUC_{t/inf}$ were 98.24% (1.03%) for Day 1 and 97.14% (1.07%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for $AUC_{t/inf}$ were 99.31% (0.41%) for Day 1 and 98.66% (0.89%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for $AUC_{t/inf}$ were 97.73% (1.24%) for Day 1 and 98.01% (1.45%) for Day 4. The mean $AUC_{t/inf}$ greater than 80% for all analytes, both on Day 1 and Day 4 indicated that the duration of sampling was sufficient.

[000162] The total amount excreted in urine (0-t hours) was calculated for each subject and analyte (except for P5P baseline corrected data). The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for Ae_{0-t}

were 848625 ng (72.13%) for Day 1 and 558650 ng (74.20%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for Ae_{0-t} were 18583712 ng (37.13%) for Day 1 and 21011635 ng (21.38%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for Ae_{0-t} were 172950596 ng (38.45%) for Day 1 and 225885311 ng (20.95%) for Day 4.

[000163] The time to reach the peak concentration was determined for each subject and analyte. The P5P (baseline corrected and uncorrected) results are summarized in Tables 6 and 8, respectively. Mean values (%CV) for the T_{max} were 0.089 h (45.25%) for Day 1 and 0.081 h (41.92%) for Day 4. The PAL results are summarized in Table 13. Mean values (%CV) for the T_{max} were 0.525 h (19.45%) for Day 1 and O.691 h (27.22%) for Day 4. The PA results are summarized in Table 15. Mean values (%CV) for the T_{max} were 0.611 h (35.24%) for Day 1 and 0.528 h (19.13%) for Day 4.

[000164] The elimination rate constant was calculated for each subject and analyte. The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for the K_{el} were 0.1381 h^{-1} (16.38%) for Day 1 and 0.1183 h^{-1} (14.41 %) for Day 4. The P5P (uncorrected) results are presented in Table 11 and. Mean values (%CV) for the K_{el} were O.1360 h^{-1} (16.60%) for Day 1 and 0.1170 h^{-1} (14.35%) for Day 4. The PAL results are presented in Table 13. Mean values. (%CV) for the K_{el} were 0.2064 h^{-1} (12.70%) for Day 1 and 0.1775 h^{-1} (13.27%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for the K_{el} were 0.3092 h^{-1} (17.01 %) for Day 1 and 0.2547 h^{-1} (20.59%) for Day 4.

[000165] The apparent half-life was calculated for each subject and treatment day. The P5P (baseline corrected) results are presented in Table 9. Mean values (%Cv) for the $T_{½\ el}$ were 5.14 h (17.65%) for Day 1 and 5.96 h (14.33%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for the $T_{½\ el}$ were 5.22 h (18.00%) for Day 1 and 6.02 h (14.14%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for the $T_{½\ el}$ were 3.40 h (12.11%) for Day 1 and 3.96 h (13.56%) for

Day 4. The PA results are presented in Table 15. Mean values (%CV) for the $T_{½ el}$ were 2.30 h (19.38%) for Day 1 and 2.83 h (23.55%) for Day 4.

[000166] Total body clearance was calculated for each subject for P5P (baseline corrected and uncorrected), The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for the CL_T were 2.55 L/h (14.75%) for Day 1 and 2.42 L/h (15.82%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for the CL_T were 2.55 L/h (14.92%) for Day 1 and 2.42 L/h (15.92%) for Day 4.

[000167] Renal clearance was calculated for each subject and analyte (except baseline corrected P5P). The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for the CL_R were 0.00279 L/h (63.53%) for Day 1 and 0.00174 L/h (44.71%) for Day 4. The PAL results are presented in Table 13. Mean values (%CV) for the CLR were 0.85952 L/h (43.20%) for Day 1 and 0.72392 L/h (27.23%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for the CL_R were 8.61246 L/h (49.20%) for Day 1 and 10.75339 L/h (20.36%) for Day 4.

[000168] Volume of distribution based on the terminal phase was calculated for each subject and analyte. The P5P (baseline corrected) results are presented in Tables 6. Mean values (%CV) for the V_β were 18.59 L (10.05%) for Day 1 and 20.75 L (19.65%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for the V_β were 18.82 L (10.03%) for Day 1 and 20.92 L (19.36%) for Day 4. The PAL results are presented in Tables 10. Mean values (%CV) for the V_β were 4.35 L (50.05%) for Day 1 and 4.21 L (38.82%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for the V_β were 28.61 L (49.49%) for Day 1 and 44.45 L (33.63%) for Day 4.

[000169] The mean residence time was calculated for each subject and analyte, The P5P (baseline corrected) results are presented in Table 9. Mean values (%CV) for the MRT were 3.40 h (20.68%) for Day 1 and 3.99 h (16.84%) for Day 4. The P5P (uncorrected) results are presented in Table 11. Mean values (%CV) for the MRT were 3.45 h (21.20%) for Day 1 and 4.03 h (16.93%) for

Day 4. The PAL results are presented in Table 13. Mean values (%CV) for the MRT were 4.06 h (17.24%) for Day 1 and 4.74 h (20.29%) for Day 4. The PA results are presented in Table 15. Mean values (%CV) for the MRT were 3.85 h (15.94%) for Day 1 and 4.24 h (21.69%) for Day 4.

Secondary Parameters Specific to Day 4

[000170] The minimum or through concentration was obtained for each subject and analyte on Day 4. The P5P (baseline corrected) results are presented in Table 3. Mean value (%CV) for the C_{min} was 946 ng/mL (61.50%). The P5P (uncorrected) results are presented in Table 11. Mean value (%CV) for the C_{min} was 974 ng/mL (61.89%). The PAL results are presented in Table 13. Mean value (%CV) for the C_{min} was 56.8 ng/mL (49.95%). The PA results are presented in Table 15. Mean value (%CV) for the C_{min} was 12.9 ng/mL (194.30%).

[000171] The average concentration was obtained for each subject and analyte on Day 4. The P5P (baseline corrected) results are presented in Table 9. Mean value (%CV) for the C_{avg} was 12614.42 ng/mL (28.40%). The P5P (uncorrected) results are presented in Table 11. Mean value (%CV) for the C_{avg} was 12641.59 ng/mL (28.52%). The PAL results are presented in Table 13. Mean value (%CV) for the C_{avg} was 1236.81 ng/mL (16.92%). The PA results are presented in Table 15. Mean value (%CV) for the C_{avg} was 885.04 ng/mL (16.25%).

[000172] The percentage of fluctuation was obtained for each subject and analyte on Day 4. The P5P (baseline corrected) results are presented in Table 9. Mean value (%CV) for the Fl(%) was 1734.69% (21.82%). The P5P (uncorrected) results are presented in Table 11. Mean value (%CV) for the Fl(%) was 1731.62% (21.88%). The PAL results are presented in Table 13. Mean value (%CV) for the Fl(%) was 537.81% (28.22%). The PA results are presented in Table 15. Mean value (%CV) for the Fl(%) was 482.53% (17.05%).

[000173] Area under the concentration-time curve (0-tau) was calculated for each subject and analyte on Day 4. The P5P (baseline corrected) results are presented in Table 9. Mean value (%CV) for the $AUC_{0-\tau}$ was 302742.00 ng·h/mL (28.39%). The P5P (uncorrected) results are presented in Table 11. Mean value (%CV) for the $AUC_{0-\tau}$ was 303393.72 ng·h/mL (28.51%). The PAL results are presented in Table 13. Mean value (%CV) for the $AUC_{0-\tau}$ was 29682.94 ng·h/mL (16.92%). The PA results are presented in Table 15. Mean value (%CV) for the $AUC_{0-\tau}$ was 21240.85 ng·h/mL (16.25%).

[000174] Theoretical accumulation ratio was calculated for each subject and analyte on Day 4. The P5P (baseline corrected) results are presented in Table 9. Mean value (%CV) for the accumulation ratio was 1.07 (2.62%). The P5P (uncorrected) results are presented in Table 11. Mean value (%CV) for the accumulation ratio was 1.07 (2.63%). The PAL results are presented in Table 13. Mean value (%CV) for the accumulation ratio was 1.02 (0.91%). The PA results are presented in Table 15. Mean value (%CV) for the accumulation ratio was 1.00 (0.58%).

Non-Compartmental Pharmacokinetic and Statistical Conclusions

[000175] ANOVA did not detect any statistically significant difference between treatment days for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for P5P (both baseline corrected and uncorrected) and PA.

[000176] For PAL, a statistically significant difference between treatment days was detected using ANOVA for ln-transformed AUC_{0-t}, and AUC_{0-inf} but not for C_{max}.

[000177] The mean $AUC_{t/inf}$ greater than 80% for all analytes indicated that the duration of sampling was sufficient to well characterize their kinetics. The intra-subject CVs for AUC_{0-t}, AUC_{0-inf} and C_{max} were respectively 7.56%, 7.14% and 9.84% for P5P (baseline corrected), 7.54%, 7.10% and 9.84% for P5P (uncorrected), 3.12%, 3.18% and 21.10% for PAL and 3.39%, 4.20% and 2.71% for PA.

[000178] Results of the 90% geometric confidence intervals of the ratio of least-squares means of the test to reference product of ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the range of 80.00% to 125.00% for P5P (both baseline corrected and uncorrected) and PA but not for PAL. For P5P and PA, these results suggest that with a once daily dosing regimen, accumulation is not likely to occur and changes in rate and extent of absorption (for P5P) or biotransformation (for PA) should not be significant. For PAL, while the theoretical accumulation ratio is close to 1, it becomes apparent looking at the individual concentration-time profiles that accumulation is occurring following four days of once daily dosing of P5P.

Safety Evaluation

[000179] Six (6) subjects experienced a total of 40 adverse events during this: study. Inflammation at injection site was reported by 3 subjects (50.0% of subjects). These adverse events, however, were judged by a Medical Sub-Investigator, to be associated to the procedures and were recorded as unrelated to the study medication. Of the remaining, potentially associated, adverse events reported during the study the following adverse events were reported by more than one subject: nausea, dizziness (feels dizzy and dizziness), paresthesia (feels like pins and needles on tip of first finger [right hand] and tingling in back of neck, and feels cold [right hand]) and white blood cells in urine. The remaining adverse events were reported by only one subject: low hemoglobin, feels anxious, bruise at catheter site (right hand), red blood cells in urine, muscular cramps on thighs, low neutrophils in blood, pain (both legs), lower back pain, pain in back of neck, papules on both sides of the chest, more saliva in mouth, sweating of body, fainting, abnormal taste in the mouth, and feels hot.

[000180] Nausea, dizziness (feels dizzy and dizziness), and abnormal taste in the mouth were expected adverse events. Dizziness (feels dizzy and dizziness) was reported by 2 subjects (33.3% of subjects). Nausea was reported by 3 subjects (50.0% of subjects). Abnormal taste in the mouth was reported by 1 subject (16.7%); the maximal severity was mild for three subjects (Subjects No.

01 to 04) and moderate (Subject No. 04) for one subject. No diarrhea or vomiting was reported during this study.

[000181] Clinically significant laboratory results for elevated white blood cells (WBC) in urine (pyuria) were observed for two subjects. One subject (#03) had negative results for leukocyte esterase at the time of screening and Days -1 to 3 (because leukocyte esterase was negative, no microscopic evaluation was performed at that time). On Day 4, this subject presented with + for leukocyte esterase and 3-5/HPF for WBC; on Day 5, leukocyte esterase remained at +, but WBC rose to 10/20/HPF. A follow-up test, performed approximately 11 days later yielded a normal result. The other subject (#06) presented with trace results for leukocyte esterase and 3-5/HPF for WBC at the time of screening, + for leukocyte esterase and 0-2/HPF for WBC on Day 1, and + for leukocyte esterase and negative for WBC on Day 2; however, results for leukocyte esterase were negative on Days -1 and 3. On Day 4, this subject presented with ++ for leukocyte esterase and 10-20/HPF for WBC; on Day 5 leukocyte esterase had diminished to + and WBC to 5-10/HPF.

Conclusions

[000182] No serious, severe, or significant adverse events were reported during this study_ Upon conclusion of the clinical portion of the study, the results from the post-study laboratory tests, physical examinations, vital signs measurements, and ECGs confirmed the absence of significant changes in the subjects' state of health. Overall, the safety profile of this formulation established in this clinical trial demonstrates that the product is well tolerated with no serious or lasting treatment related effects.

[000183] Results of the 90% geometric confidence intervals of the ratio of least squares means of the test to reference product of ln-transformed AUC_{0-t}> AUC_{0-inf} and C_{max} were within the range of 80.00% to 125.00% for P5P (both baseline corrected and uncorrected) and PA but not for PAL. For P5P and PA, these results suggest that with a once daily dosing regimen, accumulation is not likely to occur and changes in rate and extent of absorption (for P5P) or

biotransformation (for PA) should not be significant. For PAL, while the theoretical accumulation ratio is close to 1, it becomes apparent looking at the individual concentration-time profiles that accumulation is occurring following four days of once daily dosing of P5P.

What is claimed is:

1. A lyophilized formulation of pyridoxal 5'-phosphate having been prepared by lyophilizing a frozen sterile aqueous solution of pyridoxal 5'-phosphate in a concentration higher than a supplement concentration and sodium hydroxide.

2. The lyophilized formulation according to claim 1, wherein the pH of the solution is between 7.0 and 7.3.

3. The lyophilized formulation according to claims 1 or 2, further comprising mannitol.

4. The lyophilized formulation according to any one of claims 1 to 3, wherein the sterile solution contains about 1 to 25 % w/w pyridoxal 5'-phosphate.

5. The lyophilized formulation according to any one of claims 1 to 3, wherein the sterile solution contains about 1 to 15 % w/w pyridoxal 5'-phosphate.

6. The lyophilized formulation according to any one of claims 1 to 3, wherein the sterile solution contains about 1 to 10 % w/w pyridoxal 5'-phosphate.

7. The lyophilized formulation according to any one of claims 1 to 3, wherein the sterile solution contains about 5 % w/w pyridoxal 5'-phosphate.

8. The lyophilized formulation according to any one of claims 1 to 7, wherein the sterile solution contains about 0.1 to 10 % w/w sodium hydroxide.

9. The lyophilized formulation according to any one of claims 1 to 7, wherein the sterile solution contains about 0.5 to 5 % w/w sodium hydroxide.

10. The lyophilized formulation according to any one of claims 1 to 7, wherein the sterile solution contains about 0.5 to 3 % w/w sodium hydroxide.

11. The lyophilized formulation according to any one of claims 1 to 7, wherein the sterile solution contains about 1.5 % w/w sodium hydroxide.

12. The lyophilized formulation according to any one of claims 3 to 11, wherein the sterile solution contains about 0.1 to 15 % w/w mannitol.

13. The lyophilized formulation according to any one of claims 3 to 11, wherein the sterile solution contains about 0.5 to 10 % w/w mannitol.

14. The lyophilized formulation according to any one of claims 3 to 11, wherein the sterile solution contains about 0.5 to 5 % w/w mannitol.

15. The lyophilized formulation according to any one of claims 3 to 11, wherein the sterile solution contains about 3 % w/w mannitol.

16. The lyophilized formulation according to any one of claims 3 to 15, wherein the sterile solution contains about 5 % w/w pyridoxal 5'-phosphate, about 1.5 % w/w of the sodium hydroxide and about 2.8% w/w of the mannitol.

17. The lyophilized formulation according to any one of claims 3 to 16, wherein the sterile solution contains about 250 mg pyridoxal 5'-phosphate, about 80.5 mg sodium hydroxide and about 150 mg of mannitol.

18. An injectable formulation containing pyridoxal 5'-phosphate, reconstituted from a lyophilized formulation according to any one of claims 1 to 17, using a sterile carrier suitable for intravenous administration.

19. The injectable formulation according to claim 18, wherein the sterile carrier is water for injection.

20. A process for preparing a lyophilized formulation of pyridoxal 5'-phosphate comprising the steps:

(a) preparing a sterile solution comprising pyridoxal 5'-phosphate and sodium hydroxide, said solution having a pH between 7.0 and 7.3 ; and

(b) freezing the solution; and

(c) lyophilizing the frozen solution.

21. The process according to claim 20, wherein step (a) further comprises dissolving mannitol in the sterile solution of pyridoxal 5'-phosphate and sodium hydroxide.

22. The process according to claim 20 or 21, wherein the sterile solution contains pyridoxal 5'-phosphate in a concentration higher than a supplement concentration.

23. The process according to any one of claims 20 to 22, wherein the sterile solution contains about 1 to 25 % w/w pyridoxal 5'-phosphate.

24. The process according to any one of claims 20 to 22, wherein the sterile solution contains about 1 to 15 % w/w pyridoxal 5'-phosphate.

25. The process according to any one of claims 20 to 22, wherein the sterile solution contains about 1 to 10 % w/w pyridoxal 5'-phosphate.

26. The process according to any one of claims 20 to 22, wherein the sterile solution contains about 5 % w/w pyridoxal 5'-phosphate.

27. The process according to any one of claims 20 to 26, wherein the sterile solution contains about 0.1 to 10 % w/w sodium hydroxide.

28. The process according to any one of claims 20 to 26, wherein the sterile solution contains about 0.5 to 5 % w/w sodium hydroxide.

29. The process according to any one of claims 20 to 26, wherein the sterile solution contains about 0.5 to 3 % w/w sodium hydroxide.

30. The process according to any one of claims 20 to 26, wherein the sterile solution contains about 1.5 % w/w sodium hydroxide.

31. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 0.1 to 15 % w/w mannitol.

32. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 0.5 to 10 % w/w mannitol.

33. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 0.5 to 5 % w/w mannitol.

34. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 3 % w/w mannitol.

35. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 5 % w/w pyridoxal 5'-phosphate, about 1.5 % w/w of the sodium hydroxide and about 2.8% w/w of the mannitol.

36. The process according to any one of claims 21 to 30, wherein the sterile solution contains about 250 mg pyridoxal 5'-phosphate, about 80.5 mg sodium hydroxide and about 150 mg of mannitol.

37. A kit useful for preparing the injectable formulation according to claim 18, comprising instructions for preparing the injectable formulation and in separate containers:

(a) the lyophilized formulation of pyridoxal 5'-phosphate of according to any one of claims 1 to 17; and

(b) a sterile carrier suitable for intravenous administration.

38. The kit according to claim 37, wherein the sterile carrier is water for injection.

39. The kit according to claim 37 or 38, further comprising a container for said injectable formulation, said container sized to facilitate preparation of a selected volume and concentration of said formulation.

40. Use of a lyophilized formulation according to any one of claims 1 to 17 for the preparation of an injectable formulation suitable for administration to patient in need of treatment with pyridoxal-5-phosphate.

41. A method of treating a patient in need of treatment with pyridoxal-5-phosphate comprising intravenously administering the injectable formulation according to claim 18 or 19.

42. A method of reducing the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of the injectable formulation according to claim 18 or 19.

43. Use of a injectable formulation according to claim 18 or 19 for reduction of the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof.

44. A method of treating a patient undergoing a surgical procedure in need of treatment with pyridoxal-5-phosphate comprising intravenously administering the injectable formulation according to claim 18 or 19.

45. The method according to claim 44, wherein the surgical procedure is coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

46. Use of a lyophilized formulation according to any one of claims 1 to 17 for the preparation of an injectable formulation suitable for administration to patient undergoing a surgical procedure in need of treatment with pyridoxal-5-phosphate.

47. The use according to claim 46, wherein the surgical procedure is coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Figure 1

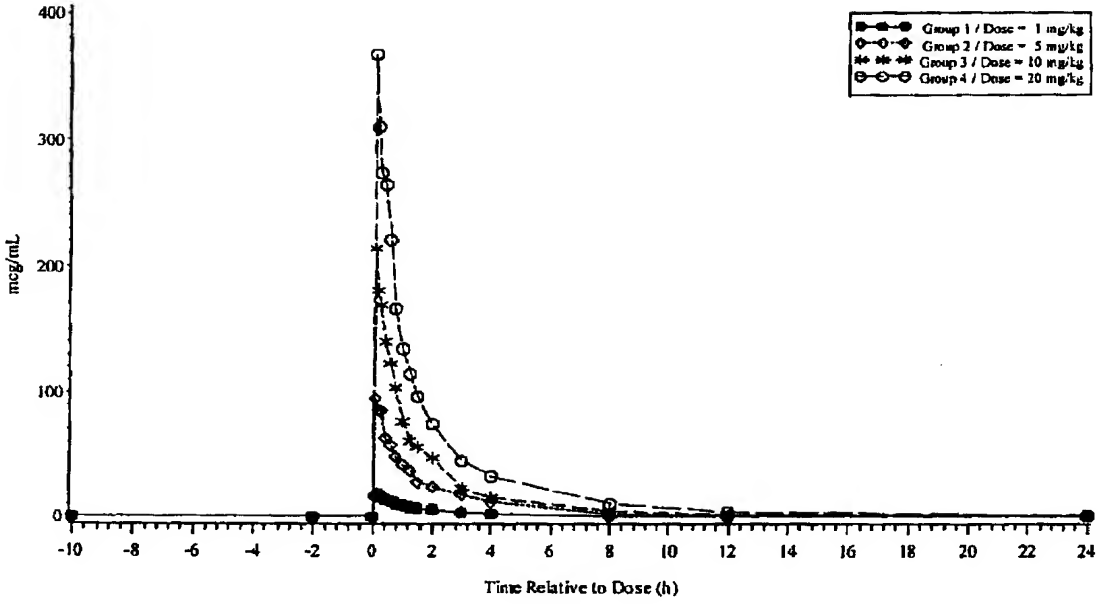

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
400
300
200
100
0
-10
-8
-6
-4
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 2

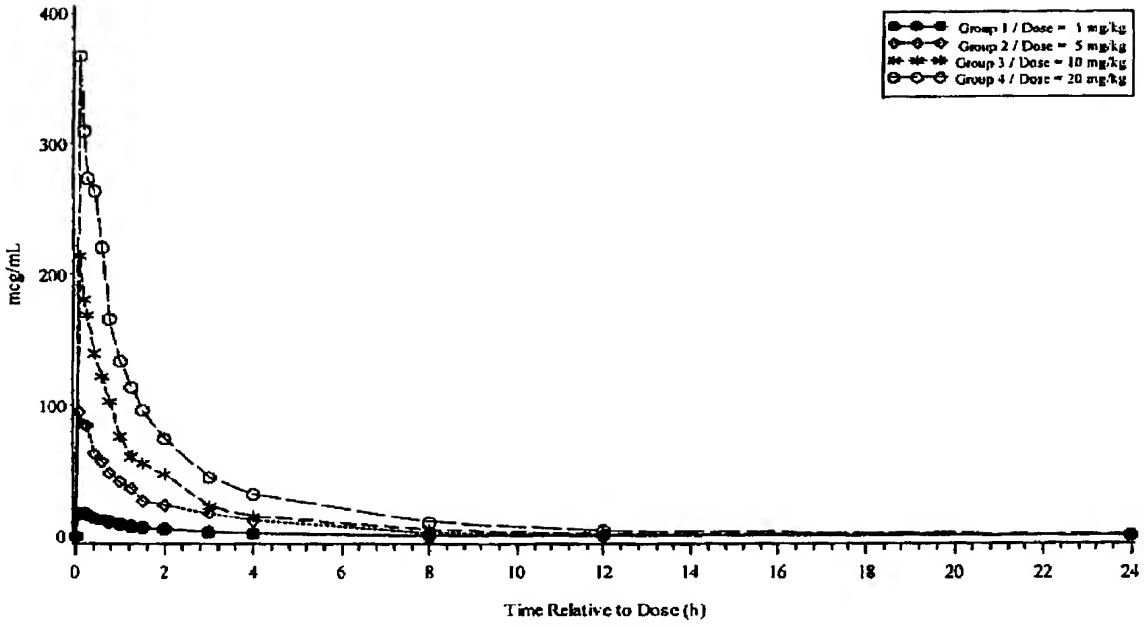

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
400
300
200
100
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 3

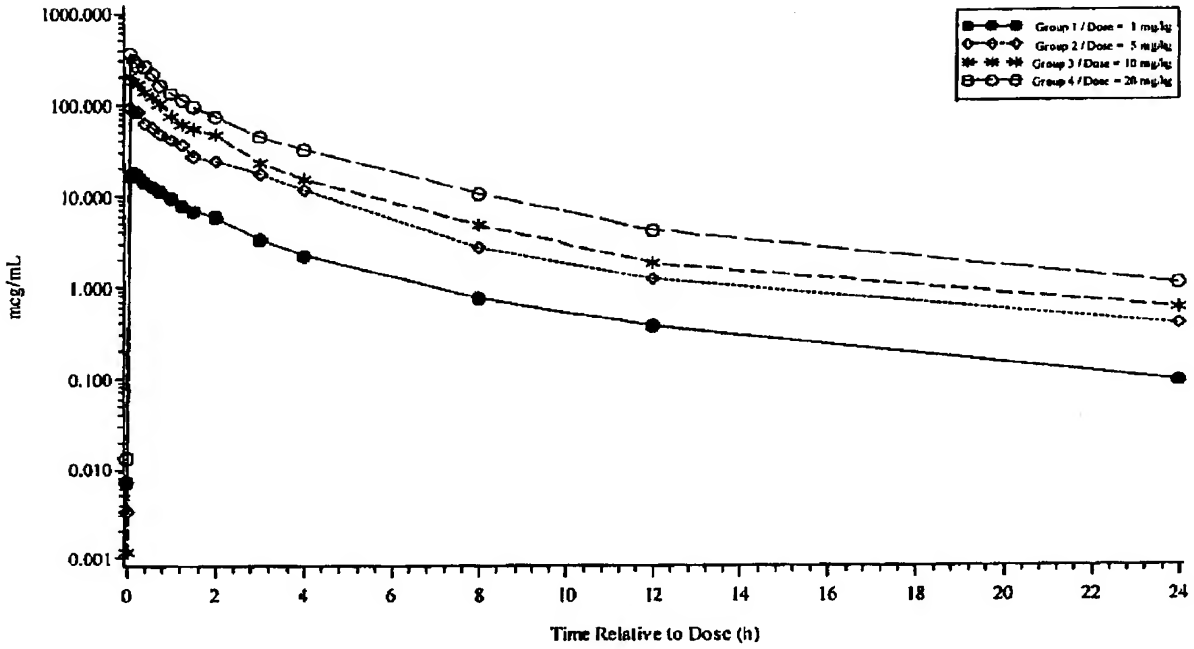

1000.000
100.000
10.000
1.000
0.100
0.010
0.001
mcg/mL
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 4

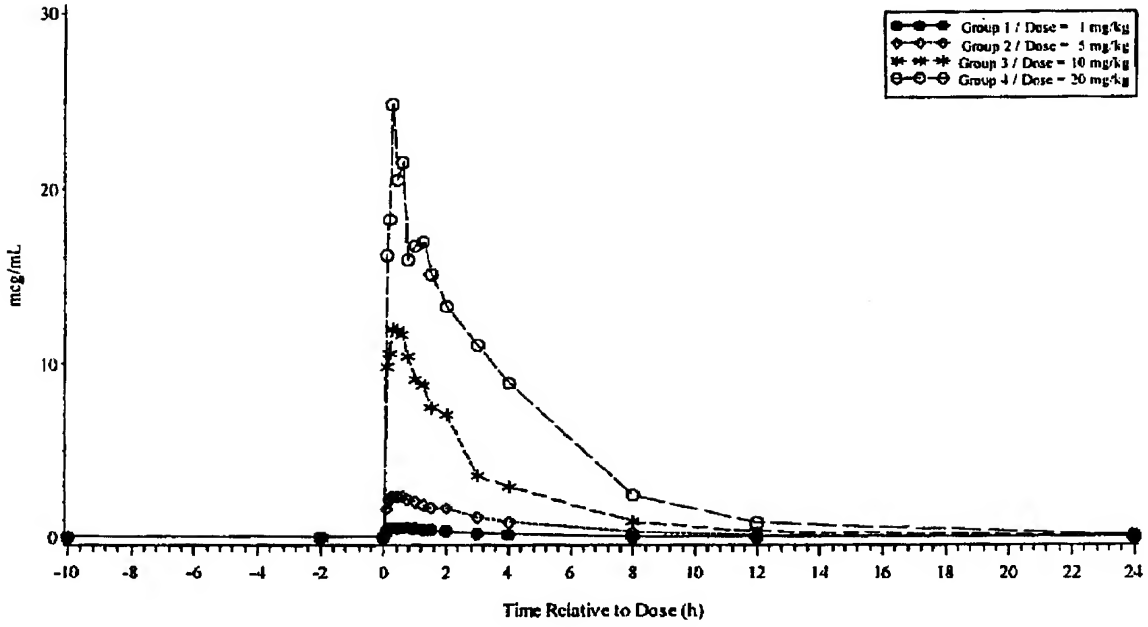

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
30
20
10
0
-10
-8
-6
-4
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 5

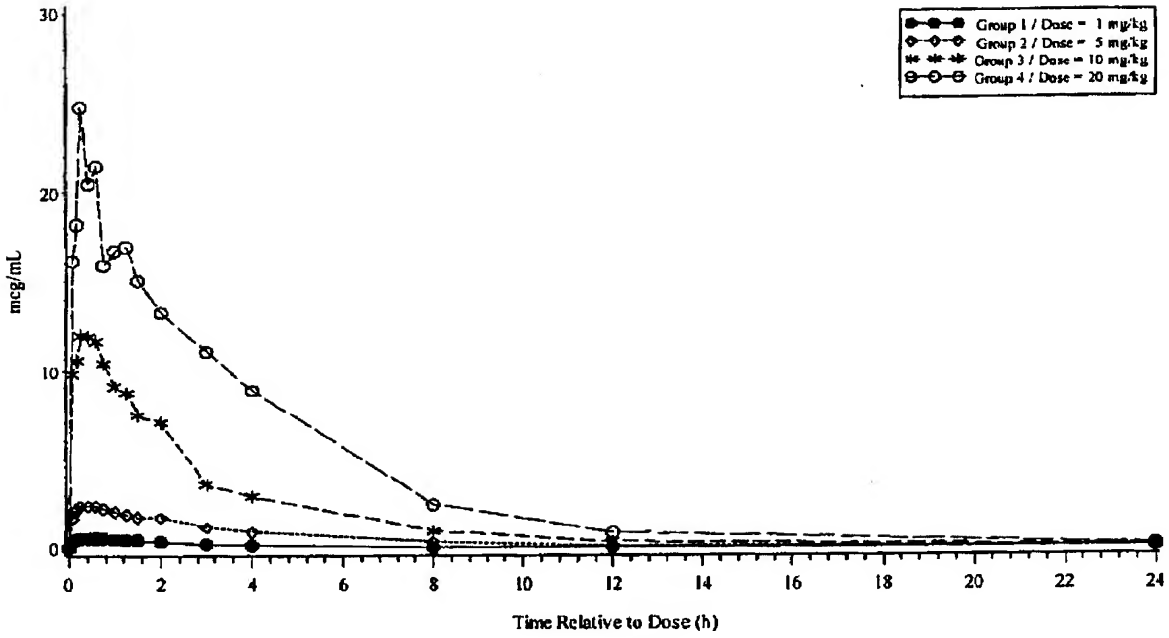

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 6

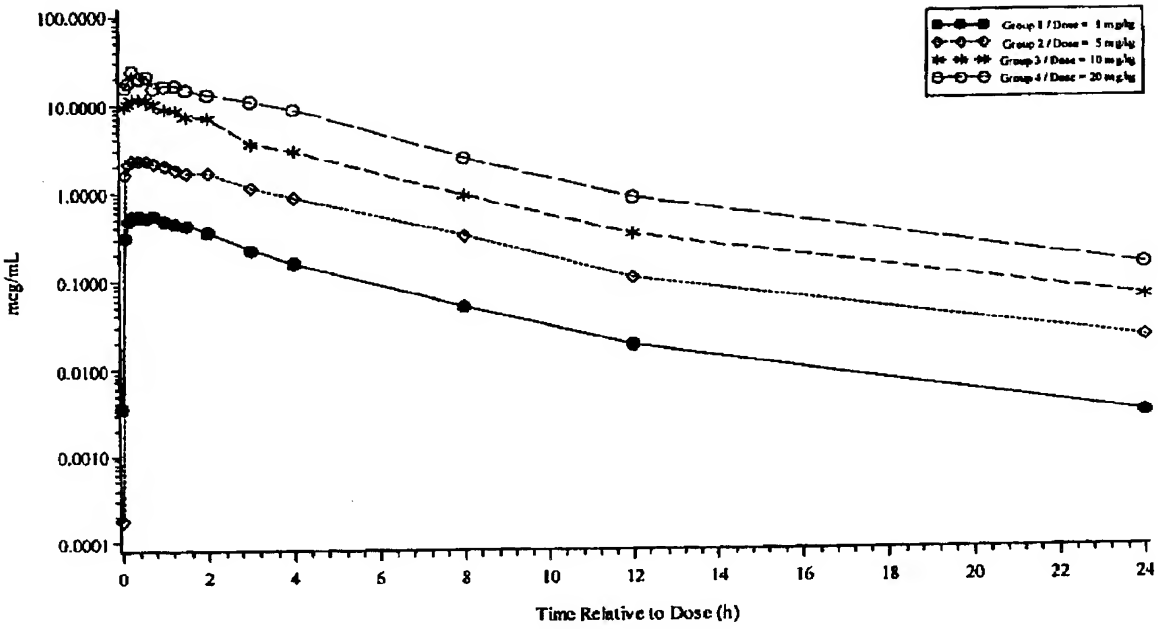

100.0000
10.0000
1.0000
0.1000
0.0100
0.0010
0.0001
mcg/mL
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 7

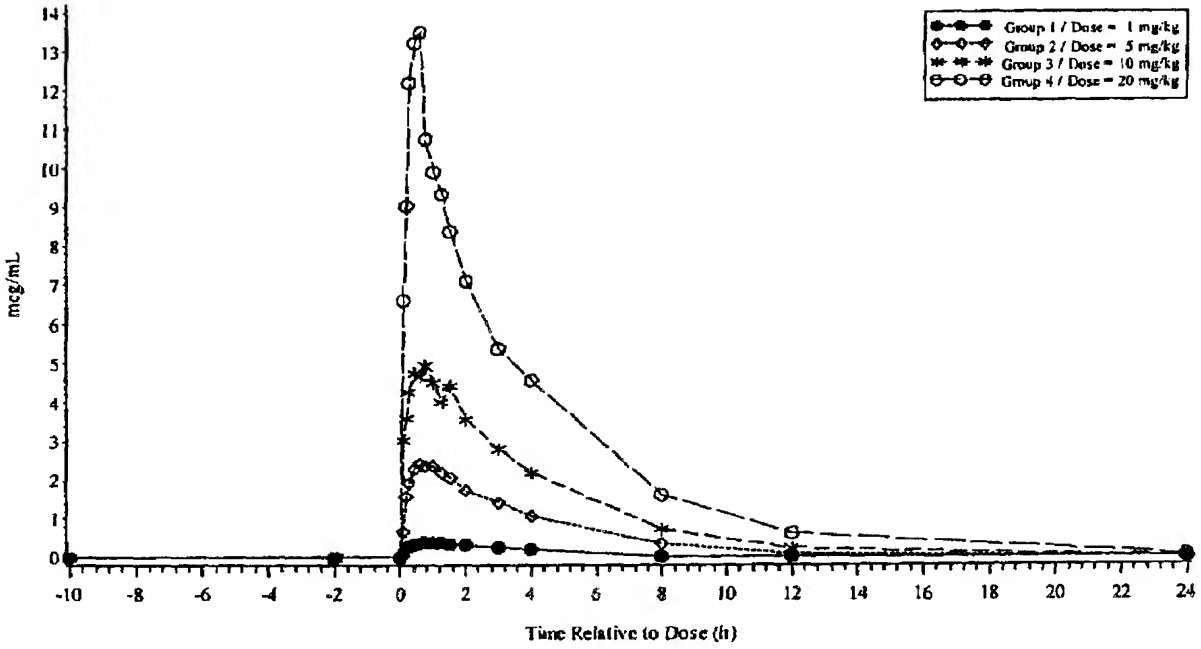

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
Time Relative to Dose (h)

Figure 8

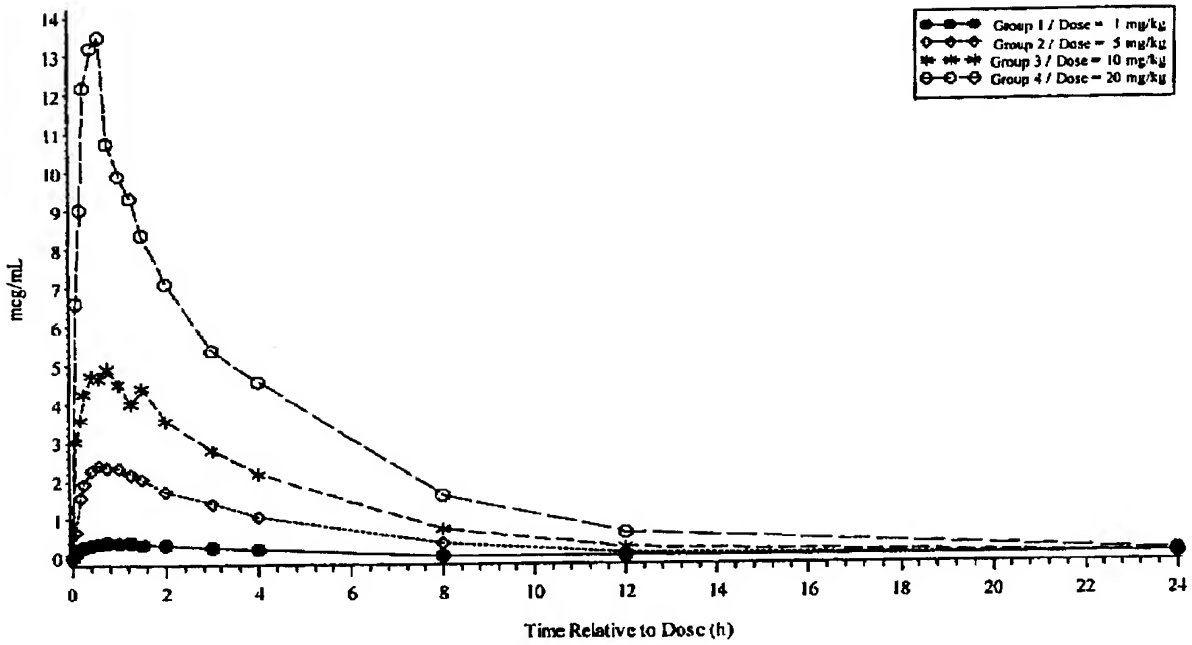

Group 1 / Dose = 1 mg/kg
Group 2 / Dose = 5 mg/kg
Group 3 / Dose = 10 mg/kg
Group 4 / Dose = 20 mg/kg
mcg/mL
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 9

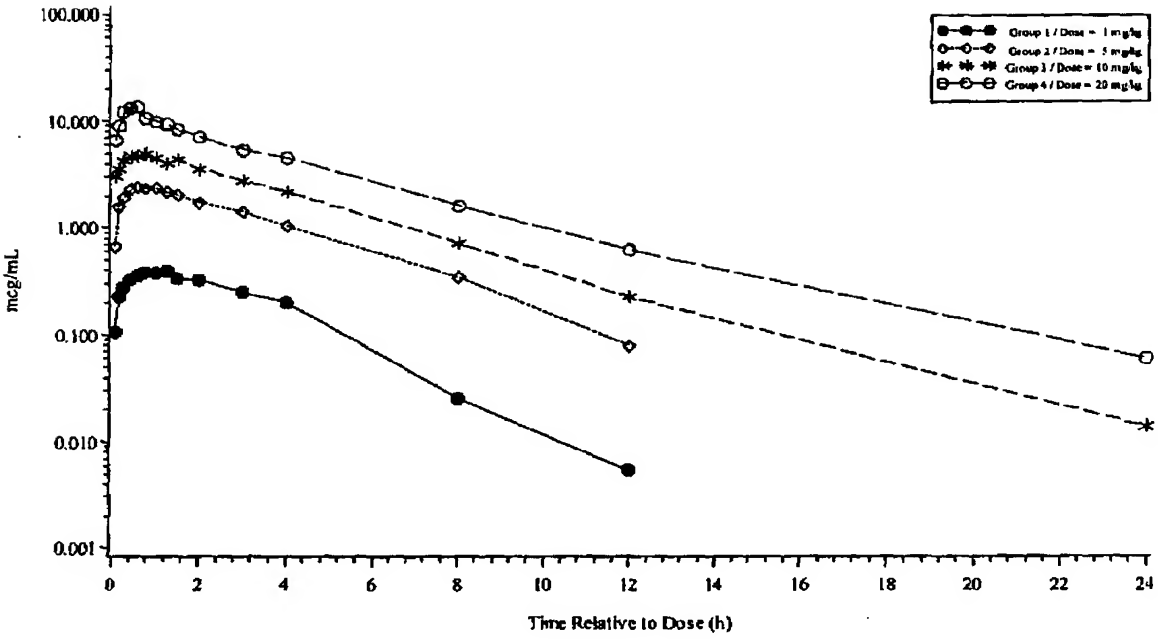

100.000
10.000
1.000
0.100
0.010
0.001
mcg/mL
0
2
4
6
8
10
12
14
16
18
20
22
24
Time Relative to Dose (h)

Figure 10

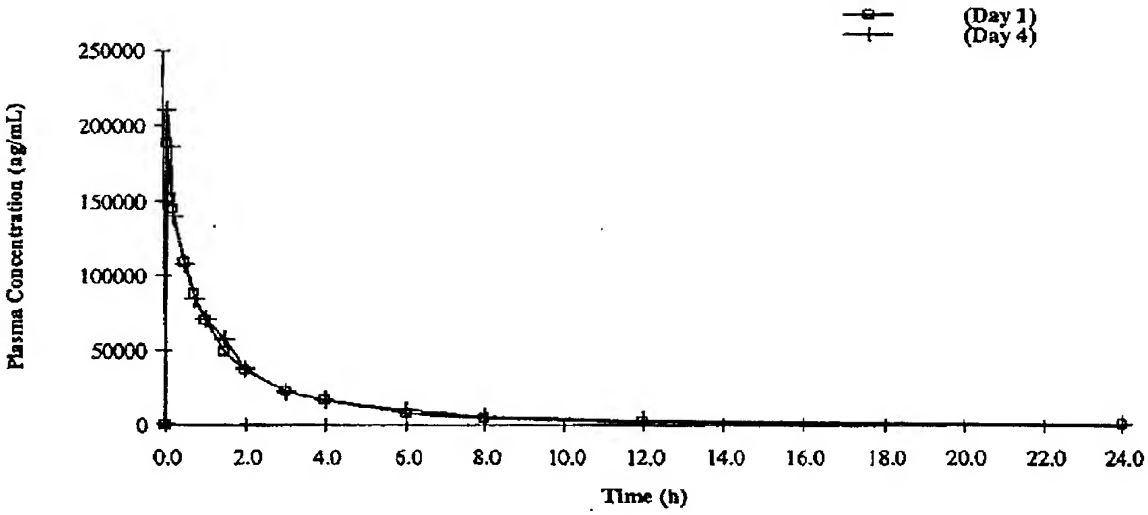

(Day 1)
(Day 4)
Plasma Concentration (ng/mL)
250000
200000
150000
100000
50000
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 11

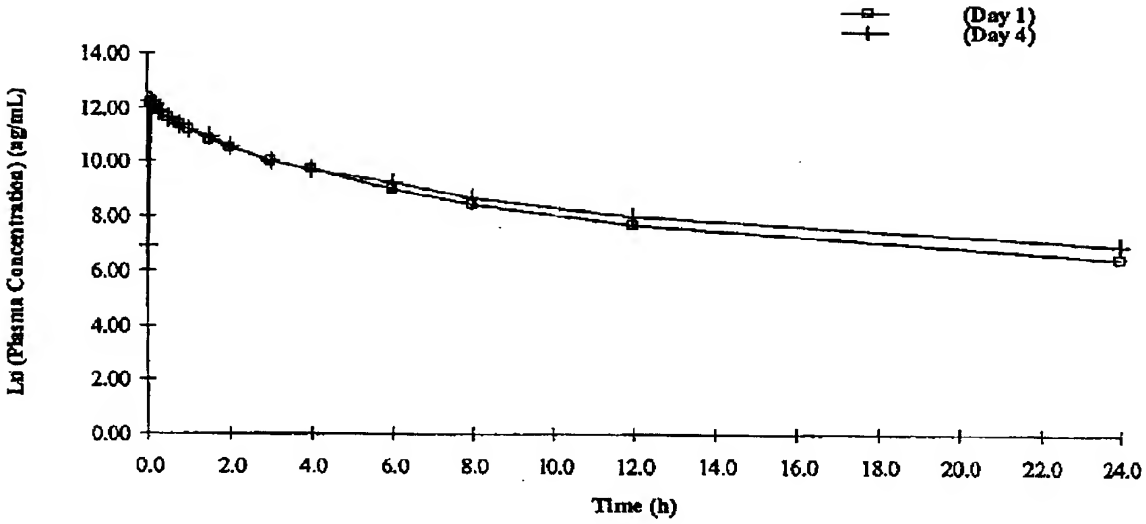

(Day 1)
(Day 4)
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Ln (Plasma Concentration) (ng/mL)
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 12

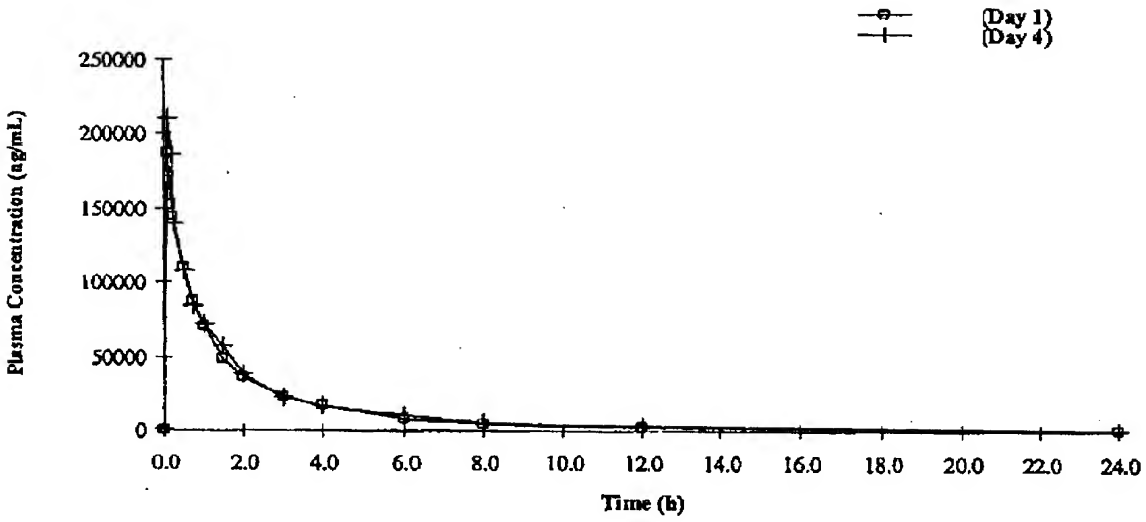

(Day 1)
(Day 4)
Plasma Concentration (ng/mL)
250000
200000
150000
100000
50000
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 13

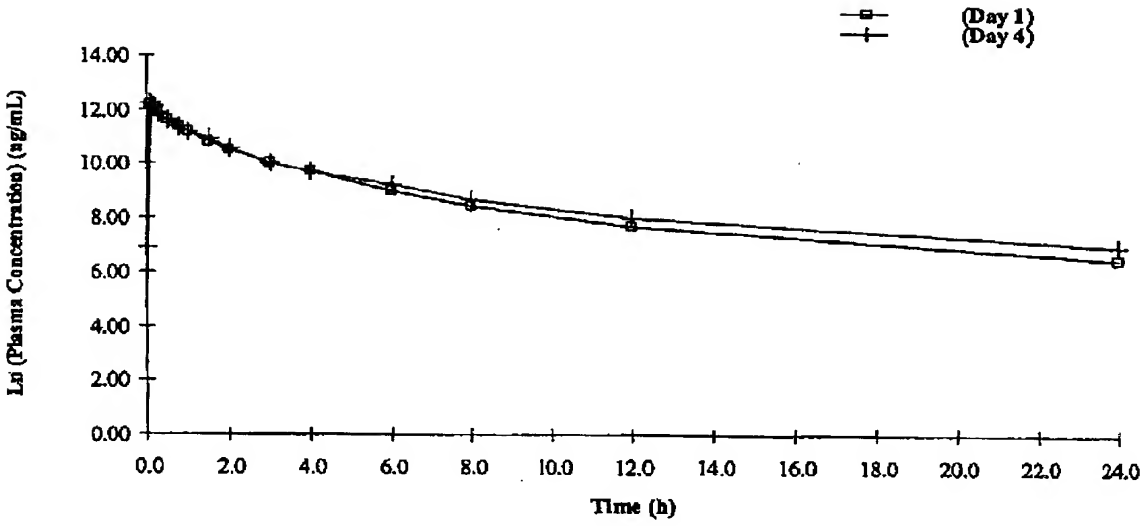

(Day 1)
(Day 4)
Ln (Plasma Concentration) (ng/mL)
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 14

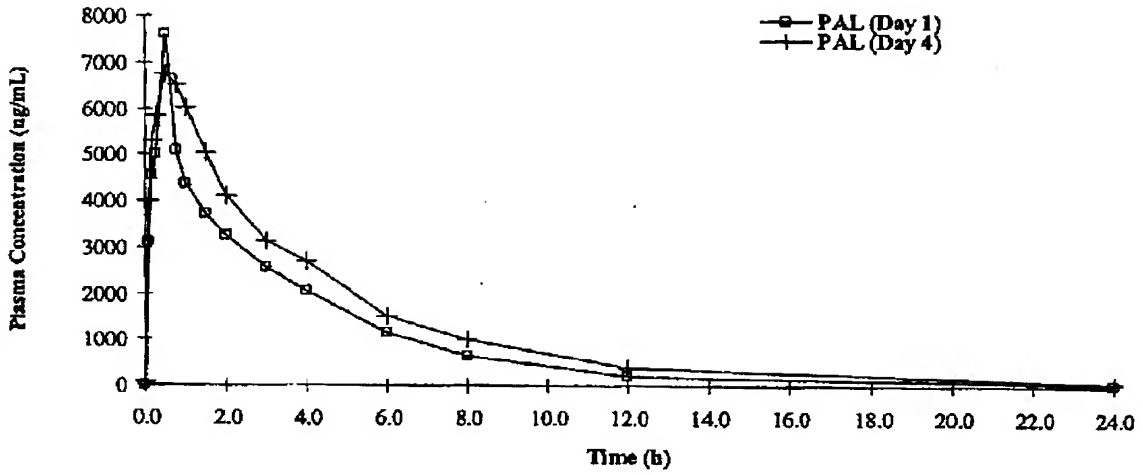

PAL (Day 1)
PAL (Day 4)
Plasma Concentration (ug/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 15

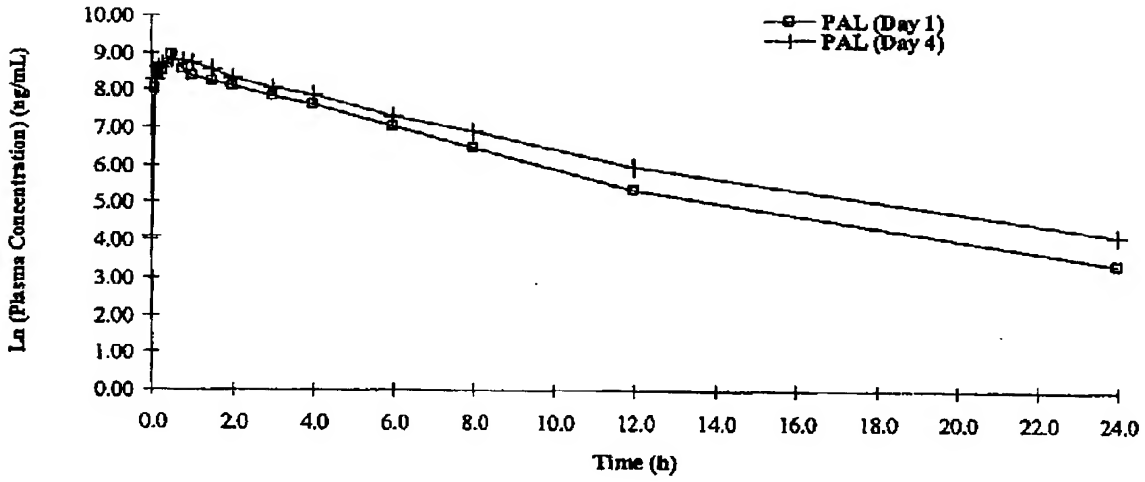

PAL (Day 1)
PAL (Day 4)
Ln (Plasma Concentration) (ng/mL)
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 16

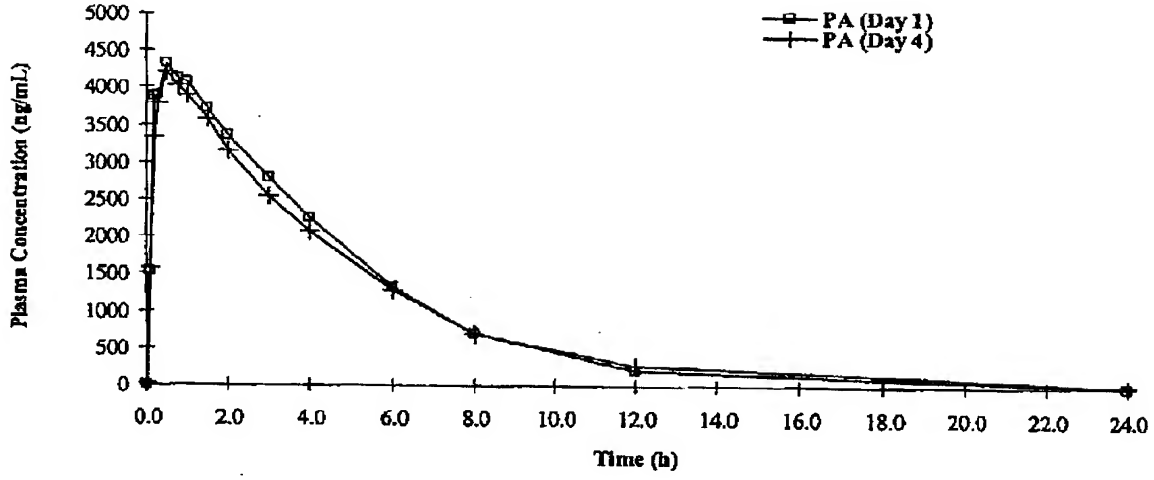
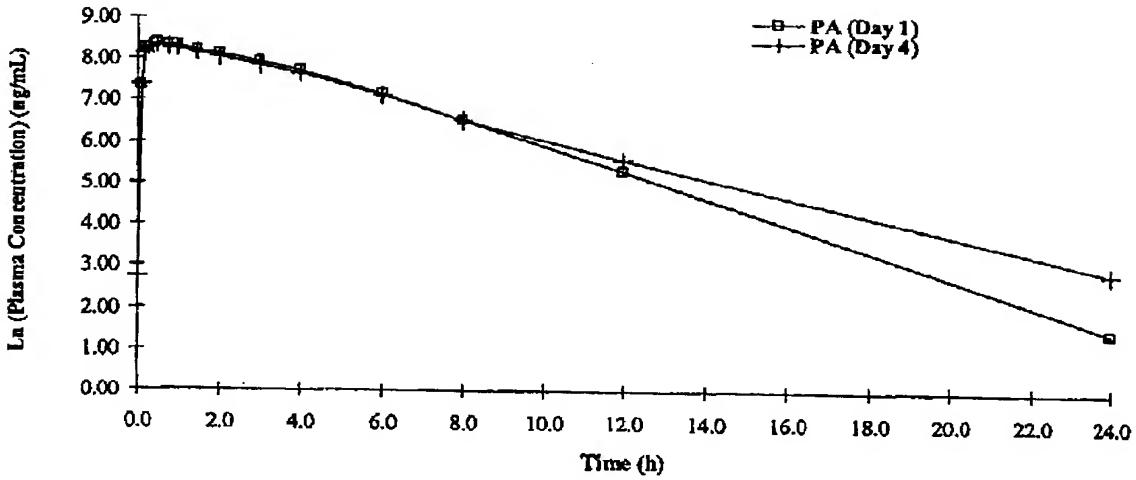

PA (Day 1)
PA (Day 4)
Plasma Concentration (ng/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

Figure 17


PA (Day 1)
PA (Day 4)
Ln (Plasma Concentration) (ng/mL)
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
Time (h)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000467

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/675*** (2006.01) , ***A61K 47/10*** (2006.01) , ***A61K 9/19*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (2006.1) A61K-31/675, A61K-9/19, A61K-47/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC (2006.1) A61K

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
PubMed & Google Scholar & Delphion & Canadian Patent Database : pyridoxal, "vitamin b6", lyophilized, freeze dried

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,411,894, (Schrank, et al.), 25-10-1983 (see column 2, lines 25-27)	1-17
Y	Pal, et al., "Uptake of Pyridoxal and Pyridoxal Phosphate by Ehrlich Ascites Tumor Cells", *J. Biol. Chem.*, **1961**, *236*(3), p894-897. (see page 894, Materials and Methods)	1-17
Y	Ihara, et al., "Stability of Fat-Soluble and Water-Soluble Vitamins in Artificially Prepared, Vitamin-Enriched, Lyophilized Serum", *J. Clin. Lab. Anal.*, **2004**, *18*:240-246. (see abstract)	1-17
A	US 6,417,204, (Haque), 9-7-2002 (see whole document)	1-17

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2006 (13-06-2006)	11 July 2006 (11-07-2006)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer
Karol Gajewski (819) 934-6734

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000467

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 41, 42, 44, 45

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 41, 42, 44, 45 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 41, 42, 44, 45.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2006/000467

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US4411894	25-10-1983	AR230178 A1	01-03-1984
		AT5508T T	15-12-1983
		AU534959 B2	23-02-1984
		AU5928980 A	08-01-1981
		CA1173360 A1	28-08-1984
		DE3065818D D1	12-01-1984
		DK155172B B	27-02-1989
		EP0021337 A2	07-01-1981
		ES492676D D0	16-05-1981
		FI72875B B	30-04-1987
		HU186296 B	29-07-1985
		IE49615 B1	30-10-1985
		IL60326 A	30-09-1983
		JP56007714 A	27-01-1981
		KR8501301 B1	12-09-1985
		MC1336 A	21-04-1981
		NO155226B B	24-11-1986
		NZ194047 A	14-09-1982
		PH16795 A	28-02-1984
		PT71436 A	01-07-1980
		ZA8003567 A	24-06-1981
US6417204	09-07-2002	AU7226301 A	21-01-2002
		CA2414188 A1	17-01-2002
		EP1299358 A2	09-04-2003
		JP2004502757T T	29-01-2004
		NZ523815 A	30-07-2004
		US6548519 B1	15-04-2003
		US6897228 B2	24-05-2005
		US2005107443 A1	19-05-2005
		WO0204421 A2	17-01-2002